FURTHER RARE DISEASES
and Debatable Subjects

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Edited by

F PARKES WEBER



S T A P L E S   P R E S S

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FOREWORD

In spite of a prejudice felt by many against the publication of single cases it is generally acknowledged that the symptoms of each individual patient ought to be examined as well as those characteristic of the disease from which he is suffering The therapeutic indications for the same symptoms or disease may differ widely according to age sex and constitutional factors in different individuals Inborn (developmental) and acquired constitutional peculiarities have often to be specially considered the presence of which is sometimes first realized by the physician on going thoroughly into the case

It is to the exact study of single cases that our knowledge of many symptoms syndromes and diseases was first due The intensive study of individual cases (especially of developmental abnormalities) often brings to light the presence of associated syndromes or diseases For instance gross developmental dysplasias may be associated with inborn metabolic peculiarities developmental mental defects and sometimes with familial allergic tendencies and abnormalities of the endocrine and autonomic nervous systems Such instances of the association of developmental conditions should be recorded including cases in which some of the associated features are not necessarily morbid for instance the exceedingly rare power of partial voluntary control over pulse and heart movements the voluntary production of abnormal ocular movements (including some forms of nystagmus) the apparent (though doubtful) power of voluntary vomiting (without any signs of illness) abnormal associated movements of various kinds the power of mirror writing (without effort in some children) the phenomena of ordinary left handedness etc

I need not here again refer to the well known arguments in favour of intensive study of rare cases namely that exceptions prove (test *probant*) the rule and that in order to be sure of the diagnosis of ordinary diseases it is advisable as far as possible to exclude the presence of rare diseases In regard to opinions that many constitutional and developmental anomalies are so rare that if one meets with them once in an ordinary lifetime one is not likely to meet with them again and that therefore one ought not to devote much time to their study I would quote a recent dictum by Prof F A Kehrer (1948) that the scientific importance of such anomalies does not depend on their frequency Indeed I have come to think that the study of such rare conditions deserves to be regarded almost as a

speciality They should be discussed at paediatric societies and at clinical and medical meetings of all kinds There might well be a *Journal of Rare Diseases and Abnormalities* founded Dr C F Hawkins has kindly drawn my attention to the following passage in Sir James Paget s writings (The Bradshawe Lecture on Some Rare and New Diseases *Lancet* 1882 2 1017) But even as they (the rare cases) are singly and in disorder let me say that we ought not to set them aside with idle thoughts or idle words about curio sities or chances Not one of them is without a meaning not one but might be the beginning of excellent knowledge if only we could answer the question Why is this rare? or being rare Why did it in this instance happen?

I wish to thank the publishers and editors of the medical journals mentioned in the various parts of this book for kind permission to reprint or otherwise to make use of published articles and letters the *British Medical Journal* the *Lancet* the *Proceedings of the Royal Society of Medicine* the *Annals of the Rheumatic Diseases* *Brain* the *Journal of Neurology and Psychiatry* the *British Journal of Dermatology* the *British Journal of Children s Diseases* the *Quarterly Journal of Medicine* the *International Clinics* and (many articles) the *Medical Press* Several of the articles which have been published elsewhere have been more or less altered and augmented

F P W

THE NECROBIOTIC NODULES OF RHEUMATOID ARTHRITIS

Case in which the scalp, abdominal wall (involving striped muscle), larynx pericardium (involving myocardium), pleurae (involving lungs), and peritoneum were affected[1]

RONALD W RAVEN F PARKES WEBER and
L WOODHOUSE PRICE

Much has been written about the nodules of rheumatoid arthritis which though present in less than a quarter of the patients may nevertheless be regarded as constituting an important if not the most important feature from the pathological point of view Collins (1937) and others including Parkes Weber (1943 1944) Kersley and others (1946) have shown that the characteristic subcutaneous nodules consist of foci of fibrinoid degeneration and necrosis surrounded by a border of tissue reaction notably by a palisade like radiate arrangement of fibroblasts Somewhat similar microscopic appearances have been described in pathological conditions of a different nature (granuloma annulare necrobiosis lipoidica) but even if the histological features of the nodules of rheumatoid arthritis were absolutely pathognomonic one would still be far from the discovery of the essential pathogenic agent

Allison and Ghormley (1931) made a great point of what they called focal collections of lymphocytes in the synovial membrane of joints being almost pathognomonic of proliferative arthritis of uncertain origin – that is to say of rheumatoid arthritis But if one looks at their illustrations (for instance p 147 fig 4 p 169 fig 3 and Plate VIII) one recognizes the presence (in these focal collections) of so called germ centres of Flemming Now surely such lymphadenoid foci with typical germ centres can hardly be considered as pathognomonic of any special disease Apart from their conspicuous presence in normal lymphadenoid tissue (lymph glands tonsils the walls of the vermiform appendix and intestines the Malpighian corpuscles of the spleen) they form a special feature in so called lymphadenoid goitres and are also not rarely found in thyroids from patients with Graves disease One of us (Parkes Weber) has seen them in abnormal salivary glands They constitute a conspicuous

[1]From *Annals of the Rheumatic Diseases* 1948 1 63

feature of cutaneous lymphocytomata (Epstein 1935) and may be found in various other pathological conditions (Parkes Weber 1947)

Similarly there *is nothing absolutely pathognomonic* in the painless lymphadenopathy of the superficial lymph glands which is present during active periods in many cases of rheumatoid arthritis though seldom noticed by the patients themselves and often not looked for by the examining doctor It is non specific follicular lymphadenopathy of toxic or infective origin with marked enlargement of the germ-centres of Flemming (not to be confused with follicular lymphoblastoma of neoplastic nature) and tends to disappear when the patient s general and articular condition improves and the disease becomes quiescent (Parkes Weber 1947 p 38 Case 4) *Rochu (1946)* thinks that this lymphadenopathy *together with the* articular changes and occasional splenomegaly indicates that what



FIG 1 —Low power view (×45) of heart nodule showing nuclear palisading and cellular infiltration external to the clear structureless zone

we in England call rheumatoid arthritis—which cannot be separated from the Chauffard Still Felty syndrome—is much more than a joint disease and that the reticulo-endothelial system is obviously involved

As to possible pathogenic relationship between rheumatoid arthritis and rheumatic fever and between their respective nodules (cf Bennett and others 1940) there has been much discussion Most of those who have studied the question apparently have come to the conclusion that the two diseases are clinically distinct and probably not due to the same (still unknown) pathogenic agent Dawson (1933) however in his Comparative Study of Subcutaneous Nodules in Rheumatic Fever and Rheumatoid Arthritis wrote These studies lend further support to the conception that rheumatic fever and rheumatoid arthritis are intimately related and possibly

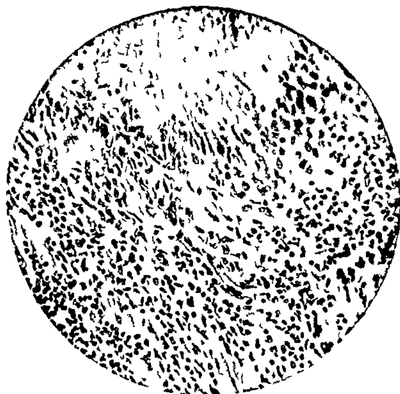


FIG 2 —High power view (x 2 0) of part of fig 1 A typical necrobiotic focus in heart muscle Note the clear structureless zone External to the latter the palisading of the nuclei and the cellular infiltration are well shown

different responses of affected individuals to the same aetiological agent

In rheumatic fever the nodules mostly remain small and soon disappear Small nodules in rheumatoid arthritis also sometimes disappear rapidly but most of the nodules especially the larger ones become chronic and are only slowly if at all absorbed – doubtless owing to the formation of the characteristic necrotic foci surrounded by chronic reactive inflammatory and firm fibrous tissue Fresh nodules may appear – a sign of renewed activity – even in old quiescent and apparently burn out cases

Case Report

History – The patient a woman aged 62 was admitted to the Royal Cancer Hospital under one of us (R W Raven) on March 14 1947



FIG 3 — Multiple necrotic foci in the pleura (× 270) These lesions are at an earlier stage of development than those shown in figs 1 and 2

on account of increasing difficulty in breathing This commenced about January 1946 and steadily progressed with increasing inspiratory stridor Eventually the patient was suffering from breathlessness whilst at rest

In April 1946 there was onset of dysphagia with special difficulty in the swallowing of fluids which were often regurgitated There was also progressive loss of voice which became more and more indistinct and of a croaking character

In December 1946 the patient noticed the appearance of multiple lumps on her head Whilst under observation similar lumps developed over the abdomen There were also nodules on the elbow joints and hands some of which probably dated from the commencement of rheumatoid arthritis in 1916

From October 1946 there was increasing difficulty in vision

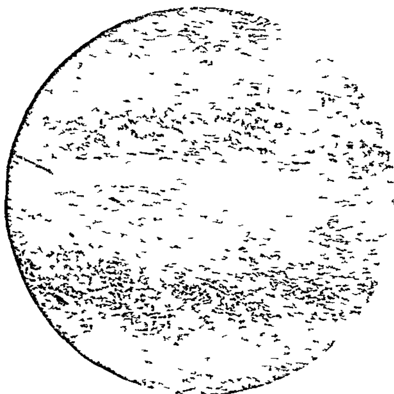


FIG 4—Confluent necrobiotic foci in heart muscle showing giant cells Low magnification (× 45)

associated with gross conjunctivitis which later progressed until by the middle of March 1947 she could only vaguely appreciate any object There was marked loss of weight and energy and the appetite was poor No symptoms related to the colon or gastro intestinal tract were noted

The patient had no children but had had five miscarriages She had had rheumatic fever in 1905 and in 1916 showed the onset of progressive chronic rheumatoid arthritis

Condition on examination —Arthritic changes involved the joints of the arms and legs with gross deformity The patient was noticed to breathe with a marked inspiratory stridor with all the accessory respiratory muscles in action There was obvious great loss of weight

Numerous nodules were present in the subcutaneous tissues of the scalp some of which were attached to the skin and some attached

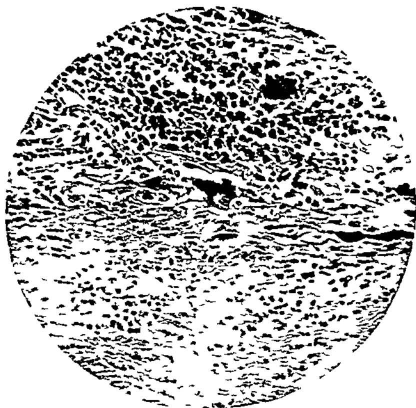


Fig 3 —Showing typical multinucleated giant cells in heart lesion under high magnification (× 220)



Fig. 6.—Another section showing similar appearances in heart lesion (× 220)

deeply to the epicranial aponeurosis. The nodules were most marked on the forehead but were scattered throughout the scalp. They varied in size from 1 cm to 3 cm in diameter.

The conjunctivae were pale and there was an extensive ulcerative scleritis with corneal involvement which in the left eye especially had the clinical appearance of a Mooren's ulcer.

There were numerous hard nodules about the elbow joints attached to the skin and on the left side ulcerated.[1]

The subcutaneous tissue of the abdomen showed multiple scattered nodules whereas none was seen over the chest.

There was a painless lymphadenopathy of the superficial lymph

[1]One of us (F. Parkes Weber) has since heard of two (unpublished) cases with ulcerated nodules of the rheumatoid arthritis type.

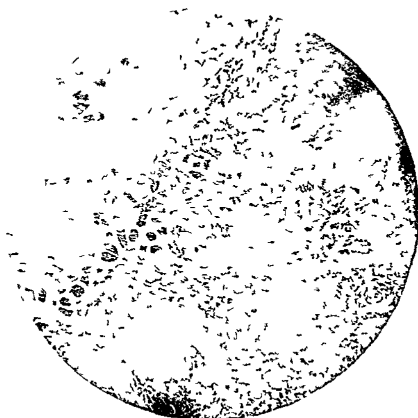


FIG 7—Showing necrobiotic changes affecting fat and heart muscle Low magnification (×45)

glands such as is often present during the active stages of rheumatoid arthritis (*see above*)

There was a patch of dry gangrene on the tip of the right great toe and no pulsation could be felt in either arteria dorsalis pedis

Radiographic investigations —Radiographs of the chest showed bronchitic changes in the lungs and some cardiac enlargement No abnormality detected on radiographic examination of the skull

There were advanced changes of rheumatoid arthritis in all the joints with marked osteoporosis and skeletal deformity A radiograph of the larynx showed a projection from the posterior wall at the level of the epiglottis

Haematology —There were 4 660 000 red blood cells and 8 000 white blood cells per c mm The Hb was 75 per cent Wassermann and

Fig 8—A focus of necrobiosis in pleura Low magnification (×45)

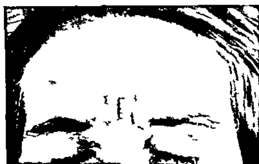


Fig 9—Nodules on the patient's forehead



FIG 10—Nodules on the patient's abdomen



FIG 11—Showing nodules on *patient's right elbow and deformity of wrist*



FIG 12—Showing gross deformity of patient's left hand and wrist

Kahn reactions were negative The erythrocyte sedimentation rate was 40 mm in one hour (Westergren)

Blood urea blood uric acid serum calcium serum inorganic phosphorus and serum phosphatase were all within normal limits There was nothing abnormal in the urine

Progress —The patient developed signs of pneumonia Her condition deteriorated and she died on March 30 1947

This patient had been seen by one of us (F Parkes Weber) who agreed that the case was one of advanced chronic nodular necrobiosis of the rheumatoid arthritis type The biopsy tissue (*see below*) had been found superficially to resemble that of a gumma

Post mortem Report

External examination —The body was that of a poorly developed poorly nourished and extremely deformed woman of about 60 years of age A small surgical incision was seen on the anterior aspect of the right temple In the left temporal region were three or four small firm circumscribed subcutaneous nodules They did not fluctuate and were not attached to the overlying skin A number of smaller nodules were seen and felt beneath the skin round the elbow and wrist joints and in the anterior abdominal wall The degree of joint deformity was considerable and the wrists and hands displayed an exaggerated ulnar deviation with wasting of the interosseous muscles presenting a picture of advanced rheumatoid arthritis In the legs it was hardly possible to move the ankle joints and the left tibia showed an almost complete backward dislocation

Internal examination —The scalp showed no abnormality apart

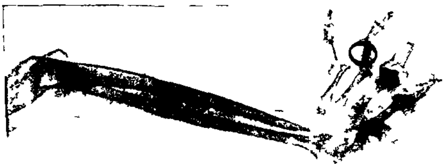


FIG 13—Radiograph showing gross deformity of left hand and wrist with osteoporosis

from that already mentioned and the skull appeared to be of normal thickness The brain was normal in appearance There was no meningitis or flattening of the cerebral convolutions The ventricles contained a normal amount of cerebrospinal fluid and the arteries at the base of the brain did not present any gross evidence of atheroma

The mouth was edentulous and the tongue larynx pharynx thyroid and trachea presented no obvious macroscopic evidence of pathological change excepting a few small submucous nodular thickenings in the region of the glottis particularly one on the epiglottis

The left lung was adherent at its apex It was partly collapsed by a left basal effusion and the visceral pleura was covered by a fairly thick fibrinous exudate The cut surface of this lung showed the characteristic appearance of collapse and there was some evidence of bronchitis Pulmonary emboli were not found

The right lung was also adherent to the parietal pleura and a small amount of turbid fluid was found at its base This lung also was covered by fibrinous exudate which had involved the media

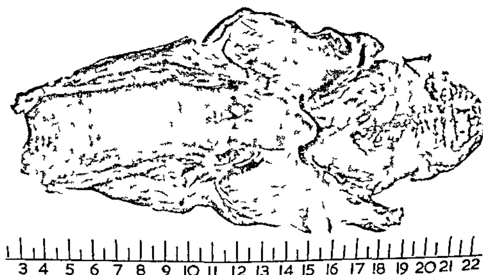


FIG 14 —Showing small nodules in glottis and particularly one rather larger one on the epiglottis

stinum and pericardium on the left side the diaphragm and the splenic capsule were involved producing an obvious perisplenitis

The pericardium was adherent over the anterior surface of the heart and on forcible removal both visceral and (to a less extent) parietal pericardia were found to be studded with raised whitish firm nodules of 1 to 10 mm in diameter There was apparently no calcification The heart was normal in size and it showed some dilatation of the left auricle with a moderate degree of mitral stenosis On the endocardial surface of the left auricle there were some nodules of



Fig 15—Heart showing multiple epicardial nodules

a similar nature to those found on the pericardium although the process in this instance appeared to be of a minor degree Further dissection of the heart was not done with a view to preserving it as a museum specimen but what could be seen of the aorta and aortic valve did not show any obvious evidence of syphilitic aortitis The heart muscle in so far as it was examined did not appear macroscopically grossly abnormal

The diaphragm was thickened by a fibrinous exudate which although penetrating on the left side to involve the spleen had not produced on the right side any noticeable peri hepatitis

The liver was normal in size Its cut surface did not present any abnormal features and the gall bladder contained about 3 c c of bile Gall stones were not found The bile ducts were patent The gastro-

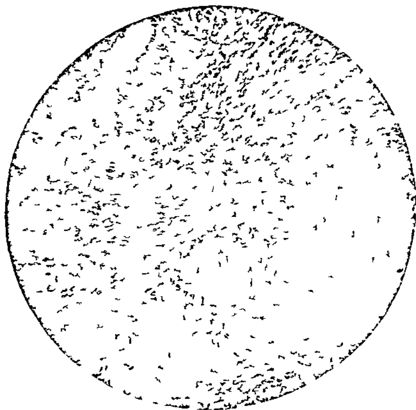


Fig 16—Nodule from larynx Lower power (×45) Several giant cells are discernible Palisading indistinct

intestinal tract appeared normal throughout The adrenals were normal

The kidneys were normal in size and the renal pelves showed no evidence of pyelitis the capsules were easily stripped off showing some degree of granulation of the kidney cortex The ureters and urinary bladder appeared normal

The uterus and ovaries together with their ligaments did not show any abnormal features

Cause of death —The cardiac condition was thought to have been the cause of death

Summary of naked eye pathological findings —Naked-eye pathological examination showed pericarditis endocarditis and mediastinitis bilateral pleural effusion perisplenitis and rheumatoid arthritis



FIG 17 —Part of fig 16 under high power (×220)

Histological Examination

Lung and pleura —The latter showed fibrous thickening in which there were several areas of necrosis of varying size from about 0 1 mm up to 5 mm These showed some peripheral palisading of nuclei but in general the appearances were not so characteristic as in the nodules in the heart muscle Giant cells were inconspicuous

In sections stained with orcein much fragmentation of elastic fibres by the necrotic process was discernible

Rectus abdominis muscle —This showed very clearly demarcated necrobiotic nodules Muscle bundles were separated and in several instances the sarcolemma sheath was either destroyed or invaded by proliferating cells

Heart muscle —Sections stained with Van Gieson showed interstitial fibrosis of the muscle fibres partly in association with necrobiotic nodules but more frequently remote from the immediate vicinity of such nodules In addition there was some deposition of calcium salts The nodules in the heart muscle were sharply demarcated and of characteristic appearance the peripheral zone of radiating fibroblasts being particularly clear

A careful search of the heart muscle remote from the necrobiotic nodules failed to reveal any characteristic Aschoff s nodes in the perivascular zones

Spleen —The splenic pulp was markedly congested and the arterioles showed well marked hyaline degeneration of their medial coats Some perivascular fibrosis was present and slight athero matous changes were seen A notable feature was the presence of multiple confluent areas of necrobiosis in the thickened capsule These presented the characteristic morphology of the necrobiotic nodules of rheumatoid arthritis though giant cells were incon spicuous The Malpighian bodies were prominent

Liver —Brown atrophy was present and there was a mild degree of cloudy swelling Certain area showed congestion but there was no gross pathological change No fibrosis was discernible other than a mild degree in certain portal areas

Kidney —The cortex showed patches of fibrosis and lymphocytic infiltration associated with glomerular sclerosis and arteriolar sclerosis The renal tubules showed well marked stellate lumina produced by cloudy swelling

Brain and pituitary —These showed no gross pathological change

Larynx epiglottic nodule —The sagittal section in the midline was passed through the epiglottis and base of the tongue

Microscopic examination showed multiple foci of necrobiosis in the sub epithelial zones of the epiglottis and also in the musculature of the tongue These foci presented the characteristic histological picture as described in the note on the general histology of these nodules (*see* further on) Several areas showed hyaline degeneration Nuclear hyperchromia and pyknosis were well marked Nuclear palisading was present and giant cells of the Touton type were frequent The characteristic lesions were well marked among mucin secreting accessory salivary glands The involved tongue musculature showed interstitial fibrosis atrophy and hyaline change

Nodules from the forehead —A nodule from the forehead (biopsy) showed necrobiotic foci surrounded by reactive cellular areas containing multi nuclear giant cells (some of Touton type)

Histology of the nodules —Characteristically the change was multi focal Typical lesions from the heart muscle showed numerous minute foci of necrosis These were approximately 0 5 × 1 mm in diameter The central zone showed pyknosis karyorrhexis karyolysis and a fine powdery deposition of calcium salts

External to this there was a narrow zone where all structure was lost and which remained almost unstained by eosin Immediately external to this structureless zone there was some cellular concentration which tended to show palisading of the nuclei and which gave the general effect of cells radiating centrifugally from the central necrotic area The cells concerned comprised lymphocytes plasma cells histiocytes and small multi nucleated giant cells Some of the latter were of Touton form with a more or less complete peripheral ring of hyperchromic nuclei others bore a slight resemblance to the tuberculous giant cell

These centres of necrobiosis were in some cases isolated and occurred in small groups each separated from its neighbour by normal adipose or muscular tissue In other instances the necrotic foci became confluent giving rise to elongated and tortuous masses which presented the characteristic histological features from within outwards as above described

We are greatly indebted to Professor D S Russell for the following report

The specimens received had been fixed in formaldehyde and consisted of (1) a portion of heart muscle with pericardium measuring 2 8 × 1 1 × 1 cm The pericardium was expanded by two opaque greyish white firm nodules the larger of which measured 0 7 cm The muscle showed no naked-eye changes (2) A portion of skin and sub

cutaneous tissues from the elbow measuring 3 2 × 1 4 × 1 cm Beneath the skin lay a nodular mass 1 4 cm in diameter of firm opaque greyish white tissue of tough somewhat fibrous consistency

One half of each specimen was embedded in paraffin wax frozen sections were prepared from the remainder and were stained with Sudan III Unstained frozen sections were mounted for examination with polarized light

Microscopic examination

(1) *Heart* —The visceral pericardium is everywhere thickened by a slight increase of collagenous fibres sparse infiltration with small lymphocytes and plasma cells and an increase in small blood vessels which are engorged There is great focal expansion of this layer by three nodules The largest shows a large central acellular area of serpiginous outline much of it appears fibrinoid but in places especially towards the periphery there are many delicate collagenous fibres and in places ill defined granular areas packed with fragmented leucocytes This acellular central area is surrounded by a dense zone of short spindle and angular polymorphic cells with round oval rod or occasionally lobed nuclei and abundant basophil cytoplasm These cells are often arranged as a palisade their long axes radiating towards the central area Small multinucleated giant cells are occasionally present There are no foam cells The cells are supported by delicate collagen fibres which in places coalesce to form small hyaline foci At the periphery of the nodule is an indefinite zone of infiltration with small round cells blending with that in the remainder of the pericardium

Frozen sections stained for fat show sparse fine extra-cellular granules throughout the central necrotic area Intra cellular droplets of larger size are numerous within the cells immediately surrounding the necrosis thereby rendering the zone conspicuous under low powers of the microscope None is to be found in the periphery of the nodule

With polarized light some of the intracellular Sudanophil material appears doubly refractive but the central extra cellular granules are isotropic

The myocardium shows in the interstitial tissue at the extreme edge of the block a nodule resembling the largest focus in the pericardium It is almost completely surrounded by bundles of muscle fibres but from the curvature of the section it must lie close beneath the pericardium The muscle is normal apart from granules of lipofuscin at the poles of the fibre nuclei

(2) *The subcutaneous lesion* from the elbow expands the dermis and is composed of aggregated nodules of varying size separated by narrow strands of connective tissue The largest nodules measuring up to 8 mm are central and are composed almost entirely of hyaline collagenous tissue Many areas are devoid of cells elsewhere sparse fibroblasts separate the fibres Near the centres of these larger nodules there are however a few ill defined acellular fibrinoid foci occasionally containing angular spaces The margins of these foci contain delicate collagenous fibres

Eight smaller nodules occupying the periphery of the conglomerate mass are lenticular and are far more cellular Though all are rich in collagen the fibres are more delicate Central necrosis of a fibrinoid character is visible in six and the general appearances in these are closely similar to those already noted in the pericardium Several giant cells of Touton type are present in one of the remaining nodules and in the compressed adjacent tissues of the dermis which show a diffuse mainly perivascular infiltration with lymphocytes plasma cells and large mononuclear cells *A few of the giant cells unassociated with nodules are conspicuously foamy but apart from these no foam cells are present* The infiltration extends about the appendages to the deep borders of the overlying epidermis The walls of blood vessels are unaltered

In frozen sections the large hyaline nodules are for the most part devoid of Sudanophil material but finely granular aggregates occupy areas corresponding to the necrotic fibrinoid foci they are associated with large unstained acicular and rhomboid cholesterol crystals In the smaller nodules the amount and distribution of Sudanophil lipoid corresponds to that already described for the pericardium

With polarized light there is abundant doubly refractive lipoid in the areas where crystals are present Unfortunately few of the smaller peripheral nodules are represented in those present the amount of doubly refractive lipoid appears somewhat greater than in the pericardial nodule

Discussion

A case like our present one in which the main feature during the latter part of the patient's life consisted in the almost universally distributed (both superficial and viscera) characteristic nodules of the rheumatoid arthritis type makes one wonder whether rheumatoid arthritis should not be classified with the infective granulomata together with tuberculosis syphilis and lepra though the infective

agent still remains unknown A varying allergic like reaction towards the infective agent (whatever it may be) almost certainly plays an important part in the symptomatology

In regard to the involvement (in the present case) both of skeletal striped muscle (abdominal wall) and of heart muscle it is interesting to study the paper by Steiner and others (1946) on Lesions of Skeletal Muscles in Rheumatoid Arthritis These authors describe a condition of nodular polymyositis in cases of rheumatoid arthritis which together with a kind of perineuritis constitutes they claim an essential lesion in rheumatoid arthritis for which they propose the term nodular neuromyositis The size of the nodules varied from those easily seen by naked eye inspection in stained sections to very small (microscopic) ones Lymphocytes and plasma cells were abundant mast cells occasional and polymorphonuclear cells and eosinophils rare or absent All the various lesions of rheumatoid arthritis they regard as of an inflammatory and granulomatous nature The muscular lesions they find differ from those found in other diseases They obviously differ in degree from the relatively gross necrobiotic nodules in our case

As to the pericardial and heart lesions in the present case one may remember that clinical signs of heart involvement of some kind are found in a great many cases of rheumatoid arthritis at various periods of the disease Feiring (1945) reported an incidence of 29 per cent (carditis) in twenty seven cases of rheumatoid arthritis It may be remembered that in Still s disease which is an infantile or juvenile type of rheumatoid arthritis Still himself reported the occurrence of pericarditis

Incidentally our case illustrates a point urged by Steiner and others (1946) namely that in old quiescent and apparently burnt out cases of rheumatoid arthritis one can never be sure that the disease may not burst out again with renewed virulence

One may ask whether a case like the present may be related to certain rare conditions classed as examples of disseminated lupus erythematosus a disease according to Baehr and Pollack (1947) expressing itself morphologically as a fibrinoid degeneration of the collagen of the connective tissues This they say is but the structural symptom of the disease whose essential nature is yet to be disclosed These authors speak of areas of fibrinoid degeneration in the subendothelial connective tissue of the epicardium which are responsible for pericarditis of the pleura responsible for pleuritis of the peritoneum responsible for peri splenitis or peri hepatitis In

our present case we found no verrucose endocardial lesions of the so-called Libman type nor the vascular lesions mentioned by these authors Clinically indeed commencing dry gangrene of the right big toe was noted but unfortunately the corresponding blood vessels were not examined post mortem

Finally in regard to lipoidal changes connected with the nodules a lipoidosis of some kind may undoubtedly be associated with symptoms and lesions of rheumatoid arthritis As in the present case and cases described by Fletcher (1946) and Kersley and others (1946) there may be and probably usually is lipoid material present in the necrobiotic nodules of rheumatoid arthritis type Professor Russell is convinced that the Sudanophil substances present in the nodules of our cases are no greater in amount nor different in character from what one might expect in such lesions with central necrosis Secondly there are rare cases which may be termed lipoid rheumatism or xanthomatous rheumatism (Parkes Weber and Freudenthal 1937 Parkes Weber 1943 and 1948 Layani 1939 Layani and others 1939) Graham and Stansfeld (1946) described an exceedingly puzzling case as one of A Hitherto Undescribed Lipoidosis simulating Rheumatoid Arthritis

Addendum January 1948

Since this paper was completed one of us (F Parkes Weber) through the kindness of Dr G B Dowling has seen a middle aged man with a typical nodular lesion over the left ulna near the elbow of the rheumatoid arthritis type The patient likewise had a ringed swelling resembling granuloma annulare over the knuckle of the right index finger This like the elbow lesion had gradually developed during the last two years Both lesions were subcutaneous and situated over prominent bones and both felt to palpation as if they consisted of multiple small nodules each nodule probably representing a minute necrobiotic focus surrounded by an area of inflammatory and fibroblastic reaction There had also been pain in muscles and joints Dr Dowling had seen two similar cases suggesting that at least some cases of granuloma annulare are of the same nature as the nodular lesions of rheumatoid arthritis with a similar aetiological factor not merely a histological resemblance Even when characteristic arthritic symptoms are absent nodules of the rheumatoid arthritis type and granuloma annulare may perhaps both be regarded as incomplete forms of what one might term the rheumatoid arthritis syndrome

Summary

A case of rheumatoid arthritis is described in which the characteristic necrobiotic nodules were of extensive distribution Arthritic changes involved the joints of the arms and legs with gross deformity and typical lesions were found in the larynx in the muscles and in the subcutaneous tissues Moreover the internal organs including the lungs pleurae pericardium and heart muscle showed macroscopic nodules of characteristic histology

Attention is drawn to the fact that some of the necrobiotic lesions were associated with giant cells but that they were not universally present

We have unfortunately overlooked the mention of a similar case of widely disseminated rheumatoid arthritis nodules with pericardial and pleural involvement (Bennett and others loc cit)

Our thanks are due to Mr S O Aylett F R C S Surgical Registrar to the Royal Cancer Hospital for helpful suggestions and to Professor Dorothy S Russell Pathologist to the London Hospital for most valuable help in the histological examination of the nodules We also thank Miss Hunt for the clinical photographs Mr Chadwin for histological preparations and Mr Cowles for photomicrographs

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II

A CASE OF JUVENILE RHEUMATOID ARTHRITIS WITH SCLERODACTYLIA AND CALCINOSIS[1]

PHILIP ELLMAN and F PARKES WEBER

An unmarried woman of 28 years was admitted to the Rheumatic Unit St Stephen s Hospital on March 15 1948 under the care of Dr Philip Ellman complaining of inability to stoop to straighten



Fig 1—The patient in May 1948

[1]From *Annals of the Rheumatic Diseases* 1948 7 231

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Fig 2—Dorsal aspect of patient's hands showing chronic remnants of juvenile rheumatoid arthritis together with early sclerodactylia and calcinosis



Fig 3—Palmar aspect of hands showing calcinosis nodules



Fig 4—Calcinosis nodule on inner side of right knee (There is an exactly similar one at the corresponding position near the left knee)

Fig 5—Radiograph of hand showing calcareous deposits

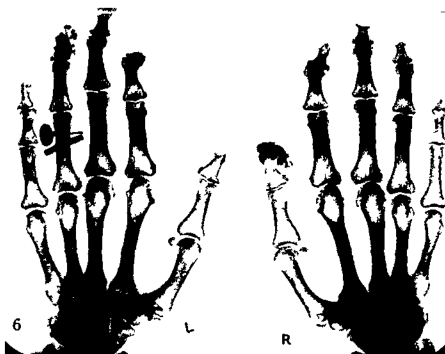


FIG 6—Radiograph of hands (for comparison) from a case of typical sclero dactylia with calcinosis (without rheumatoid arthritis) showing characteristic absorption of tips of the terminal phalanges

the elbows and to walk up high steps and also of pain on moving the elbows fingers knees and hips all for the previous seventeen *years*

At the age of 11 years she had had a painful throat and enlarged glands in the neck with high fever After a few weeks these symptoms all subsided

After a symptom free interval of a week or two her fingers became stiff and little nodules appeared on the dorsal aspects of both meta carpi her knees were stiff and swollen and she also had pain in both hips In six months this second set of symptoms cleared up Her doctor however making a retrospective diagnosis of rheumatic fever ordered her complete rest for a year and this she had sitting in a wheel chair motionless and with the elbows and knees continually immobile in 90 degrees flexion At the end of the year these joints were fixed

She then (when aged *12* or *13* sixteen or fifteen years ago) was seen by Sir Frederick (then Doctor) Still who diagnosed Still s disease and

sent her to Woodhall Spa for physiotherapy A partial recovery ensued she could walk again and go to school

At 14 years of age nodules appeared also on the medial aspects of both knees and they and the former ones began to discharge

Since then her condition has been more or less static If anything the joints are all looser but the nodules which are tender are more troublesome than before Two years ago the left forefinger being ankylosed and an encumbrance was amputated

Direct questioning reveals that her maximum weight was 6 st 2 lb one year ago now she weighs 5 st 11 lb Her menarche was at the age of 17 periods now lasting five or six days with a twenty-eight day cycle They are regular and painful In cold weather her hands go numb and white

Past and family histories show nothing of significance

Present Condition

Physical examination shows a thin young woman (fig 1) with a pleasant though somewhat immature personality and with poorly developed secondary sexual characteristics

There is apparently slight sclerodermic contraction round the mouth as well as in the hands Calcareous nodules some ulcerating the skin are seen on the fingers of both hands (figs 2 and 3) the medial surfaces of the knees (fig 4) and the medial sides of the first metatarsophalangeal joints Symmetry is a feature of these calcinosis nodules She has a slightly funnel type of sternum The left forefinger has been amputated Her spine is flattened and rigid Elbows wrists and hips (and to less extent the knees) show moderately severe limitation of all movements The finger movements are also impaired

The cardiovascular system is normal

The respiratory system shows no abnormality save poor but symmetrical movements

The abdomen is normal there being no splenomegaly and so is the nervous system There is no enlargement of any superficial lymphatic glands

Special investigations have shown nothing abnormal with the important exception of X ray examination which reveals calcinosis of the hand and wrists (fig 5) as well as some minor widespread old rheumatoid arthritic changes there is some osteoporosis at the elbows

Blood chemistry shows nothing abnormal in regard to calcium

phosphorus phosphatase urea and uric acid The blood count is normal and the erythrocyte sedimentation rate now normal The blood Wassermann reaction is negative and there is no achlorhydria The urine is free from albumin and sugar and is sterile on culture

Discussion

The case is now a typical one of slight symmetrical sclerodermia of the sclerodactylia type associated with well marked circumscribed calcinosis nodules of fairly symmetrical distribution in the extremities (cf Atkinson and Weber 1938) As in most cases of sclerodactylia *symptomatic Raynaud like phenomena have been noted* in the hands which by the way in the present case are the sites of most of the calcinosis nodules Calcinosis nodules are apparently not related to the necrobiotic nodules of the rheumatoid arthritis type (Weber 1948)

But it is the occurrence of sclerodactylia on the basis of juvenile rheumatoid arthritis – Still s disease – as diagnosed by Sir Frederick *Still himself* when the patient was *12 or 13 years old* that we wish to consider The association of mild sclerodactylia like changes with the changes of old Still s disease seems not extremely rare

For the sake of contrast we show a radiograph of the hands (fig 6) of a woman aged 76 years kindly referred to one of us (P Ellman) by Dr D Seth Smith The calcinosis of her hands is accompanied by well marked sclerodactylia without rheumatoid arthritis and the radiograph shows absorption of the tips of the terminal phalanges which is a rather rare but very characteristic feature of some cases of sclerodactylia

On the whole it seems to us probable that rheumatoid arthritis is due to some infective agent possibly a virus but until the cause of the disease is discovered its relation to occasionally associated conditions such as Raynaud s phenomena sclerodactylia (with or without calcinosis) Sjogren s disease (on the non ocular features of Sjogren s disease – *see* Weber 1945) and even rheumatic fever can be noted but the nature of the association can be only surmised Compare also Ellman (1947) especially with regard to the possible role of allergy towards a virus or other infective agent

Such surmisal would of course be aided by comparative observation and statistical enquiry on a large scale Before the infective agent of syphilis had been discovered there were some who already surmised that tabes dorsalis was due to the same cause as the ordinary primary and secondary manifestations of syphilis Just as with the

discovery of the syphilitic spirochaete it was suddenly proved that tabes dorsalis dementia paralytica and ordinary aortic aneurysms were all due to the same infection (syphilis) so when the essential cause of rheumatoid arthritis has been ultimately discovered the relation of rheumatoid arthritis to various other conditions (whether already surmised or not) will probably become evident

Summary

A case is described of typical calcinosis circumscripta—mainly of the hands—with mild sclerodactylia and Raynaud s phenomena arising on the basis of juvenile rheumatoid arthritis (Still s disease) Cases of juvenile rheumatoid arthritis associated with mild sclerodactylia are not extremely rare but in such cases of old Still s disease combined with mild sclerodactylia typical calcinosis circumscripta has apparently been seldom if ever observed

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III

SJOGREN'S DISEASE WITH DRYNESS OF THE BRONCHIAL MUCOSA AND UNCERTAIN LUNG LESION[1]

PHILIP ELLMAN and F PARKES WEBER

HENRIK SJOGREN of Jonkoping (1933 and later) by the careful study of cases of kerato conjunctivitis sicca has succeeded in establishing the existence of a syndrome or rather a disease which in its complete form includes kerato-conjunctivitis sicca xerostomia rhinitis sicca pharyngitis sicca and laryngitis sicca but the disease is far more often incomplete The eye lesion need not be the presenting condition and patients may first seek medical advice because of enlargement of salivary glands or because of xerostomia The chronic inflammatory changes in the parotid glands usually without suppuration but with recurrent exacerbations tend to produce permanent enlargement sclerosis or atrophy in irregular combination Analogous changes occur in the other salivary glands and in the oral mucosal glands and also in the lacrimal glands though usually without obvious clinical enlargement It seems certain that many cases have been labelled as Mikulicz s disease or Mikulicz s syndrome The skin especially the sweat glands and the stomach (acid producing glands) may be involved in some cases The clinical onset often more marked on one side than the other is intermittent and insidious The patients are mostly middle aged women Clinical accompaniments may include accelerated blood sedimentation rate alterations in the blood count body temperature and blood sugar curve and not rarely arthritic symptoms (rheumatoid arthritis)

In regard to the eye condition Sjogren concluded The morbid changes appear to find their simplest explanation in the fact that owing to intense diminution or complete abolition of the lacrimal secretion the conjunctiva itself is obliged to provide for the entire secretion of fluid As the result of this a chronic oedema arises which gradually leads to degeneration and atrophy of the epithelium One may suggest an analogous explanation for the secondary changes in the oral mucosa when they arise in cases of chronic xerostomia of any nature According to Sjogren s investigations it seems clear that the dryness of the mouth and eyes are preceded by changes (microscopical) in the salivary and lacrimal glands

Non ocular features of the disease (Weber 1945) in addition to the

[1]After *British Medical Journal* 1949 1 304

changes in the salivary glands and mouth may include Dryness in the nose pharynx and larynx secondary dysphagia (Plummer Vinson syndrome) secondary cough (from dryness of mouth and pharynx) achlorhydria dryness of skin dryness and atrophic change in vagina almost complete alopecia accelerated blood sedimentation rate hypochromic anaemia low blood pressure low blood sugar low blood calcium Raynaud like blueness of hands and feet telangiectasis on lips and tips of fingers telangiectatic and pigmentary scleroderma like changes in the legs (Sheldon 1938) delusional mental symptoms and occasional epileptic fits (Sheldon 1938) But some of these features may possibly be regarded as superadded conditions not directly connected with the Sjogren s disease However in regard to the curious pigmentary scleroderma like dermatosis in Sheldon s case one of us (Weber 1945) has heard of another case of Sjogren s disease with similar leg pigmentation

In the present case the unusual feature is the presence of dryness of the bronchial mucosa with some radiological basal pulmonary shadowing of uncertain nature which may perhaps be interpreted as an infected (granulomatous) atelectasis due to breakdown of the natural defence owing to the dry bronchial mucosa

Case

The patient is a delicately built woman of medium height aged 34 years (on November 13 1948) thin but apparently not losing weight Her father died at 57 of heart failure he suffered from bronchitis Her mother died at 69 of sugar diabetes The parents had 8 children of which the patient is the seventh all the others are said to be living and healthy The patient herself has always been thin and delicate looking and since the age of 13 years has been subject to short Raynaud like attacks in the fingers – the tips turn white and then blue – relieved by putting the hands into hot water She had measles at 17 and scarlet fever at 21 Whilst still in the fever hospital after the scarlet fever she developed temporary swellings on both sides of the face which were considered possibly mumps About 1940 she noticed peculiar dryness of the lips and mouth which she did not get rid of In January 1942 painless cherry sized parotid swellings developed one on each side and were diagnosed as Mikulicz s disease For these she received deep X ray treatment at the Cancer Hospital (6 seances) and they disappeared but not the dryness of the mouth

Menstruation which commenced at 12 years of age has remained

normal She married in February 1939 and in December 1943 a child (boy) was delivered by Caesarean section owing to the presence of a uterine fibroid which was removed at the same time The boy was normal at birth and has remained healthy After suckling him for 8½ months she developed two small painless lumps (September 1944) one on each side under the lower jaw With deep X ray treatment (6 séances) they disappeared She received further deep X ray treatment in February 1946 but now for the past eighteen months she has had *a small painless swelling in the right sublingual region* About September 1944 her eyes felt hot dry and irritable and a doctor told her she had conjunctivitis It cleared up but has returned on and off ever since

In April 1946 she suffered from dry pleurisy first on one side and then on the other For this she was in bed for three weeks only but never got rid of the dry cough and since then has never felt quite well Since then also the eyes have been drier and in February 1948 they became much worse and follicular conjunctivitis was diagnosed

In May 1948 a stiff neck was followed by painful swelling in the knuckles and pain and stiffness in wrists knees feet and left shoulder with some fever This polyarthritis of the rheumatoid arthritis type for which she was referred to one of us (P E) by Dr W Edwards of Ashtead and treated at the Leatherhead Hospital has now nearly subsided Her dry cough has become much worse and when she is talking she has to sip water frequently to relieve the dryness

Present Condition

She complains of dryness of eyes mouth and throat and irritable dry cough much worse on talking Sometimes she has slight difficulty in swallowing Most of her teeth have been extracted By palpation *with the finger and thumb a painless cherry sized swelling can be* felt below the tongue to the right of the middle line There is slight symmetrical enlargement of the thyroid gland but there is no clinical evidence of thyrotoxicosis

Blood-count (August 14 1948) Haemogl 98 per cent erythrocytes *4 980 000 colour index = 0 99 per cent* leucocytes 6 000 Another blood count (December 31 1948) gave Haemogl 103 per cent erythrocytes 5 700 000 colour index = 0 9 per cent leucocytes 7 600 (polymorphs 81 per cent) lymphocytes 18 per cent monocytes one per cent Urine nothing abnormal Blood pressure 120/80 mm Hg Blood Wassermann reaction negative Blood sedimentation rate not raised on *June 28* 1948 when it was 5 but on September 26 it

was 22 (normal 4 to 8) Blood calcium 10 6 mgm per cent Blood phosphorus 3 9 mgm per cent Blood alkaline phosphatase 9 units There is no sputum at present There is no clinical evidence of disease of the heart abdomen or central nervous system In the lungs there is diminution of air-entry at both bases breath sounds are tubular in type at the left base and numerous dry crepitations can be heard at both bases but are especially marked at the left base X ray examination of the chest (July 11 1947) showed diminished translucency in the left lower lobe with pleural involvement On August 16 1948 there was an area of consolidation in the left lower lobe with some scattered opacities in the right lower lobe The heart mediastinum and trachea were centrally placed the left diaphragm was obscured and the heart was normal in shape size and position A further skiagram on November 30 1948 showed little appreciable change

Bronchoscopy negative except for dryness of bronchial mucosa no secretion was obtained (Mr W P Cleland St Helier Hospital Carshalton) Electrocardiogram normal

The hands show soft tissue swelling of the proximal interphalangeal joints but no bony changes nor were there any bony changes in the other joints

The following additional investigations were carried out at the Hammersmith Hospital –

Sputum showed Gram positive cocci and diphtheroids on direct smear *Staphylococcus aureus* on culture

Fractional test meal normal secretion of hydrochloric acid

Urinary excretion of 17 ketosteroids normal

Glucose tolerance test normal

Schirmer s lacrimation test showed moistening along ½ cm of the filter paper compared with 3 to 5 cm in controls

Salivation test consisting of collection of saliva for 3 minutes after chewing and swallowing fruit gave 0 8 c c whereas control subjects produced 5 to 9 c c

A heating test for sweating gave normal response

A liver biopsy (performed because pulmonary sarcoidosis had been suggested) showed normal histology

Treatment was directed symptomatically to the dry eyes dry mouth and dry bronchial mucosa As far as the eyes are concerned cod liver oil drops gave symptomatic relief Attempts were made to increase the salivary secretion by pilocarpine mecholine and physostigmine These produced no appreciable response as shown by the

salivation test An attempt was made to alleviate dryness of the bronchial mucosa in the hope that the changes at the base of the left lung might thereby be improved by keeping the patient for a fort night in a steam tent This had no beneficial effect on the respiratory condition and the patient thought that the dampness aggravated the arthritis Breathing exercises and postural drainage produced no significant result She was given vitamin A 150 000 units daily empirically as it was thought that this could not possibly do any harm and might conceivably do some good Closure of the lacrimal ducts by local diathermy was not carried out since the patient s eye symptoms were not the most troublesome The patient thinks that inhalation therapy helped her at the Hammersmith Hospital

Discussion

This case seems to be one of Sjogren s disease which we think may be regarded as a lymphoid granulomatous condition affecting especially the salivary and lacrimal glands and giving rise to dryness of the mouth and conjunctivae The presence of slight rheumatoid arthritis may be regarded as a point in favour of this diagnosis In the present instance the bronchial mucosa is specially affected and there are pulmonary lesions of uncertain nature probably granulo matous perhaps to be explained as infected atelectases Dryness of the bronchial mucosa seems as yet not to have been noted in Sjogren s disease though its occurrence might have been expected in some cases

The main salivary gland swellings have disappeared under deep X ray therapy but the dryness of the mouth and conjunctivae has increased if anything and there is a swelling in the right sublingual region Further treatment of the case beyond inhalation therapy is problematic but we think that the lacrimal ducts should now be *closed by diathermy in order to diminish the conjunctival dryness* Mikulicz s disease is a lymphoid granulomatous condition of the salivary and lacrimal glands very susceptible to X ray treatment and it is a question how far it is to be distinguished from Sjogren s disease to which perhaps it may be an allied condition (variant) The advisability of further deep X ray treatment is a question for consideration – both in regard to the sublingual nodule and the lungs

There is also the question of the lung condition being of sarcoid nature but the negative liver biopsy makes this unlikely We need not therefore consider the further question of a possible relationship

between Sjogren s disease Mikulicz s disease and sarcoidosis The replacement of glandular tissue in Sjogren s disease and Mikulicz s disease by a kind of lymphoid granulomatous tissue reminds one it may be noted of the gradual replacement of thyroid glandular tissue by lymphadenoid tissue in cases of so-called lymphadenoid goitre

We are greatly indebted to Dr J C Scadding for the investigations carried out at the Hammersmith Hospital We have to thank Dr J N Cumings and Dr S A Withers for routine clinical pathological and X ray examinations respectively

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IV

REMARKABLE SYPHILITIC CASES

F PARKES WEBER

I HAVE met with several remarkable early syphilitic manifestations all of them in absence of arsenical treatment (1) Early Syphilitic Paraplegia (with Dr Risien Russell *Brain,* 1898 **21,** 520) (2) Acute Hepatic Atrophy (*Proc Roy Soc Med* 1909 **2,** Path Section 113) (3) Early Syphilitic Non suppurative Meningo encephalo myelitis (*St Bartholomew s Hospital Reports* 1915 **50,** 157) (4) Acute Nephrosis (with Dr H Schmidt *International Clinics* 1916 26th series **1** 89) In this latter striking case when it seemed almost hope less a dramatic functional recovery took place by a diuretic crisis and the whole chronic waterlogged condition rapidly disappeared leaving of course innumerable *striae cutis distensae*

In 1907 I wrote a paper (*Lancet* 1907 **1,** 728) on tertiary syphilitic fever a condition almost unknown in England at the present time In my first patient the liver was enlarged and the fever which was of an irregular type rapidly yielded to antisyphilitic treatment

In regard to *differential diagnosis* in 1930 I recorded the fact that a temporarily positive Wassermann reaction (false Wassermann reaction) may occur in glandular fever (*Med Press* 1930 **181** 66 and *Brit Med Journ* 1930 **2** 194)

In 1908 I published a note on what one might call osteitis defor mans of inherited syphilis (*Brit Journ Child Dis* 1908 **5** 83) Children with resulting prolongation in length of the lower extremities (probably never seen nowadays) constitute strange and remarkable pictures

In 1940 with Dr T Anwyl Davies and Dr David Nabarro I wrote a short paper (*Brit Journ Child Dis* 1940 **37,** 173) headed Familial Vulnerability of Special Sites towards the Lesions of Con genital Syphilis—Ischaemic Disturbance in Fingers of Two Sisters probably due to Third Generation Syphilis It was highly probable that the mother of the patients had congenital syphilis and that the remarkable lesions in both children were due to attenuated syphilis of the third generation A point of special interest in the two sisters was that the lesion which we supposed to have been of congenital syphilitic origin and probably of ischaemic nature affected the same fingers of the same hand in both cases as if those fingers were the site of a special familial vulnerability This may be compared to

cases in which congenital syphilis in two sibs manifests itself especially in the eyes (interstitial keratitis) I remember for instance a brother and a sister both suffering from interstitial keratitis whose father had I knew died with general paralysis of the insane At a meeting of the Societe Medicale des Hopiteaux de Paris on February 12 1926 Guillain Perisson and Trevenard made a communication on a family afflicted with tabes dorsalis and nervous syphilis At the next meeting (February 19 1926) Charles Flandin described cases of familial aortic syphilis as examples of the familial predisposition of certain sites to be affected by tertiary syphilis

My paper on Chronic Fibroid Subcutaneous Syphilomata of the Legs (*Brit Journ Derm and Syph* 1920 32 173) was apparently the first to draw attention to the condition but following is a more complete account of the subject by C Worster Drought My patient it should be noted had likewise the well known condition of chronic periurethral induration in the penis suggesting that he had a special tendency to develop fibrous induration such as some persons have to develop Dupuytren s contraction of the palmar fascia or Landouzy s acquired type of camptodactylia

V

SUBCUTANEOUS FIBROID SYPHILOMATA

A Rare Manifestation of Late Syphilis

C WORSTER DROUGHT

THE condition for which Parkes Weber [1] in 1920 suggested the name 'subcutaneous fibroid syphilomata is admittedly a very rare manifestation of late syphilis Indeed so scanty is the literature of the subject that Goodman [2] on reporting a case in 1921 claimed that only two such cases had previously been recorded and further that when he and Young [3] published a case in February 1920 there was at that time no similar case in the literature

In the case here described bilaterally symmetrical lesions involved the ulnar nerves and yielded rapidly to antisyphilitic treatment

Description of a Case [4]

The patient is a woman aged 27 married three years no children and no history of miscarriage She has had a slight goitre since the age of 14 and at 12 years had an attack of diphtheria otherwise no previous illnesses She gives no history suggesting acquired syphilis

Family history —Her father died at the age of 67 having suffered for over twelve years from a condition the patient terms creeping paralysis the description of which suggests tabes dorsalis (intense pain in legs unsteady gait and loss of control of bladder) Her mother still alive has had epileptic fits (average frequency one per month) since the age of 15 An elder sister died at 30 with Graves disease one brother aged 35 has a goitre and three elder sisters are healthy

History of present condition —The patient states that during the past three months small lumps have developed on the inner and posterior aspect of both forearms they first appeared just below the elbow and gradually spread downwards towards the wrist At first the lumps were quite painless but more recently she has had neuralgic pain

Condition on examination —A series of hard subcutaneous nodules extend downwards along the inner aspects of both forearms from just below the olecranon to a point three inches above the styloid process of the ulna The nodules are bilaterally symmetrical and diminish progressively in size from above downwards those nearest the elbow being the largest and varying from 1 to 2 cm in diameter

At the lower end of the series the lesions have a diameter of only a few millimetres (fig 1 is a semi diagrammatic representation of the condition which did not show well in a photograph) The nodules are quite hard and adherent to the deeper tissues the skin over them however is freely movable The majority are quite painless on palpation and only a few situated within an inch or so of the upper limit of the series on each side give rise on firm pressure to tingling pain referred to the little and ring fingers In the deeper tissues of the upper third of the forearm just anterior to the ulna and in the region of the ulnar nerve some small nodules can be felt pressure on these also produces pain in the distribution of the ulnar nerve Over the ulnar area of each hand there is some hyperalgesia to pin prick The interossei hypothenar and adductor pollicis muscles however show good voluntary movement and react normally to faradism There is some parenchymatous enlargement of the thyroid gland with pulse rate of 76 and no signs of hyperthyroidism All other systems show no abnormal physical signs

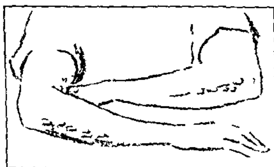


Fig 1 —Semi-diagrammatic repre entation of the condition

X ray examination of the forearms reveals some nodes on the periosteum of the ulna on both sides but not corresponding to the nodules seen and felt in the tissues

Pathology –To determine the diagnosis of the condition one of the nodules a short distance below the elbow was excised and submitted to Dr Clement Lovell for histological examination The report was as follows The small tumour which is tough and elastic on section is a gumma Sections stained with haemotoxylin and Van Gieson stain show on microscopical examination masses of fibrous

tissue separated by a looser tissue which is highly vascular The vessels in this latter area are surrounded by aggregations of inflammatory cells chiefly small round cells Some of the vessels show thickening of the intima with very little infiltration of the vessel wall other vessels show thickening of the adventitial coat with marked infiltration by small round cells (fig 2) The blood serum yielded a positive Wassermann reaction

Subsequent progress – The patient was given six intravenous injections of novarsenobillon (two doses of 0 45 two of 0 75 and two of 0 9 gramme) alternating with six intramuscular injections of mercury cream (1 grain of Hg per dose) one injection being given each week Potassium iodide (grains 10 t d s) was also taken by the mouth By the time the fourth injection of novarsenobillon was reached all pain had disappeared and there was a remarkable diminution in the size and consistency of the nodules When the last of the series of injections had been given no nodules were visible and all that could be felt was a slight induration of the subcutaneous tissue at the sites previously occupied by the nodules When seen six months later there had been no recurrence and it was even difficult to be sure of any degree of tissue thickening

Subcutaneous Syphilomata General Clinical Description

The age incidence varies between 27 and 60 years in the recorded cases and both males and females are affected The lesions consist of nodules varying in size from that of a pea to that of a chestnut The most frequent site is the ulnar border of the upper part of the fore arms the larger nodules being placed near the olecranon and in distribution they are as a rule remarkably symmetrical The nodules may also be found in the region of the knee particularly in relation to the ligamentum patellae between the patella and the anterior tuberosity of the tibia more rarely they extend downwards towards the ankle Those occurring in the lower limb are usually larger and less firm and hard than those in the upper limb In character the nodules are of fairly regular rounded or oval shape and of a peculiar wooden hardness a most unusual feature of gummata They are themselves painless and it is only when they lie in relation to a nerve as in the case reported above that any pain is experienced The skin overlying them is freely movable but they are usually adherent to deeper structures X ray examination when performed has shown no bony changes in the case described above however there were nodes on the periosteum of the ulna

which did not correspond to the nodules felt in the tissues The lesions develop slowly attaining a maximum size in a period varying from a few months to two years in different cases and then remain stationary

Their syphilitic nature is proved by the presence of a positive Wassermann in all recorded cases in which this test has been per formed and also by the histological character of the nodules—viz that of an organizing or fibroid gumma Microscopical examination

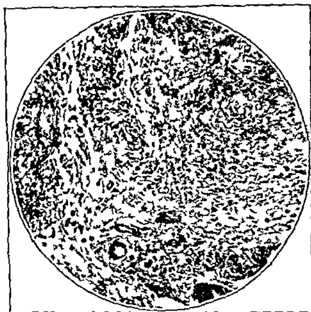


FIG 2—Section of syphiloma (×70) showing fibrous tumour surrounded by a zone of inflammatory tissue In this zone are many vessels showing endar teritis obliterans with periarteritis

shows a chronic inflammatory lesion which has become fibrous with out undergoing true gummatous or necrotic changes Goodman and Young made from a nodule a preparation by Levaditi s silver impreg nation method but *Treponema pallidum* was not found In most of the cases there has also been a history indicating syphilis—chancre miscarriages etc—and in a few other signs of syphilis—e g a tertiary syphilide in Goodman s case In the case described a congenital origin is possible the history suggesting that the patient s father had suffered from tabes dorsalis In those cases treated on modern anti syphilitic lines the nodules rapidly disappeared

Summary of other Recorded Cases

1 Goodman and Young s case [3] Woman aged 29 married No history of syphilis one abortion at the fourth month and no subsequent pregnancies Wassermann reaction positive Bilaterally symmetrical nodules extending downwards from two inches below the olecranon to the styloid process of the ulna also a single mass over left knee and in the ligamentum patellae Duration eight years Microscopical diagnosis Granuloma probably syphilitic

2 Parkes Weber s case [1] Man aged 60 Gonorrhoea at age of 20 but no *history of syphilis Wassermann reaction positive* Multiple subcutaneous nodules present on legs chiefly right and extending downwards from just above the knee to the ankle in addition one nodule was situated on the outer side of middle of right thigh Duration seven years The condition was associated with peri urethral induration of the penis (induratio penis plastica) and also old disseminated choroido retinitis of right eye Microscopical diagnosis Tertiary syphilitic lesion become fibrotic

3 Goodman s case [2] Man aged 36 History of chancre ten years previously but no secondary symptoms W R positive Two nodules were present on the right forearm below the olecranon and three on the left forearm the first of the latter was symmetrical with those on the right side the second was situated over the internal condyle and the third two inches above the olecranon On the left leg a smaller nodule was present over the tubercle of the tibia Duration eight years Over the metacarpal of right thumb there was also a serpiginous tertiary syphilide $2 \times 1\frac{3}{4}$ in Microscopical diagnosis of nodule Gumma The tumours disappeared following treatment with 12 intravenous injections of arsphenamine the less recent leaving only a slight induration

4 Howard Fox s case [5] Negress aged 45 No definite history of syphilis two children in good health and two miscarriages W R strongly positive Nodules on both forearms along ulnar borders and also in the region between patella and tuberosity of tibia on both knees Duration two years Microscopical diagnosis Organizing gumma The lesions responded slowly and imperfectly to intravenous injections of arsphenamine but the patient attended at only irregular intervals

5 In the course of his communication Howard Fox mentions another case which he observed in 1919 Negress aged 34 No history of syphilis but had three children all of whom died as infants W R positive Nodules present on olecranon and ulnar borders of both

forearms and also on both knees below the patella Duration thirteen years Microscopical diagnosis Unsatisfactory as piece of tissue was too small and patient was lost sight of

Howard Fox s communication was read at the forty fourth annual session of the American Dermatological Association Swampscott Mass in June 1921 In the subsequent discussion the following speakers mentioned that they had met with similar cases

6 T E Lane Man aged 45 Nodules on ulnar borders of each forearm near olecranon The lesions had almost disappeared after six injections of arsphenamine

7 J F Schamberg Two cases in negresses each showing symmetrical cartilaginous nodules below the elbows

8 J C Fordyce also mentioned a case of nodules on one elbow

9 C R Lane [6] Man aged 45 Alleged gonorrhoea at 20 five years later small lumps appeared over the lower part of both ole cranon processes They were small single and painless and so con tinued for more than eighteen years when following a blow the nodule on the right arm broke down and several satellite nodules appeared over the area At the same time a second nodule appeared on the left arm The blood W R was positive On biopsy the histological structure of the lesion was that of a fibrosing gumma

10 C P G Wakeley [7] Man aged 38 with small nodules on the back of both forearms for one year and gradually becoming larger for the past six months History of gonorrhoea at 18 On examina tion numerous small and painless nodules along the extensor surfaces of both forearms Blood W R positive A biopsy of a nodule showed the typical structure of a fibroid gumma The nodules disappeared rapidly on treatment with injections of novarsenobillon and mercury cream

Juxta articular Nodules

The clinical similarity of the tropical condition known as juxta articular nodules to subcutaneous syphilomata was commented upon by Goodman and Young Juxta articular nodules appear first to have been described by MacGregor and were later in 1909 studied in detail by Jeanselme [8] They occur in natives of many tropical countries including Java Siam and tropical Africa According to Manson [9] juxta articular nodules are round or oval multiple symmetrical nodules painless and very hard and increase slowly in size until they may attain the size of a small orange Broden and

Bernard s analysis [10] indicates that the nodules are more frequent in the lower limbs than the upper

In his original communication Jeanselme described juxta articular nodules as of various sizes usually globular in shape and often collected together in masses At first they lay deep in the subcutaneous tissues some freely movable and others appearing to be adherent to the periosteum from which possibly they originated Later the nodules became more superficial and might be incorporated in the skin Beyond distension and slight discoloration at the highest point the skin underwent no change The nodules were remarkably symmetrical and occupied the extensor aspects of the extremities with a tendency to surmount bony prominences and to group them selves near joints—e g in the arms about the olecranon acromial process and dorsal surface of fingers and in the legs about the great trochanter head of tibia and external malleolus Microscopically *the nodules were divisible into three zones*

1 External zone of inflammation made up of fibrous tissue numerous blood and lymph capillaries plasma and polymorphonuclear cells and large fixed cells with a fibrillated reticulum

2 Intermediate transitional zone of gradually homogenizing connective tissue which lost its fibrillar structure and stained deeply with eosin

3 Internal zone of degeneration formed of irregular homogeneous and translucent blocks Bacteriological examinations proved negative

Jeanselme considered that the nature of the nodes was not revealed by microscopical examination and that they had no relationship to syphilis tuberculosis or xanthoma nor were they fibromata nor tophi Davey [11] considered them to be a late manifestation of yaws An organism has been claimed by some to be the aetiological factor but this has been denied by others Thus Van Dijke and Oudendal (1922-23) and Soberheim (1924) claim to have demonstrated spirochaetes in the nodes Gougerot a fungus which he placed under Nocardia and Ouzilleau (1913) filarial elements (quoted by H S Stannus [12])

In 1920 Poupelain [13] in reporting 5 cases of juxta articular nodules stated that he had found they were rapidly cured by novarsenobillon injections and drew further attention to their possible association with syphilis In the same year Montel [14] described 4 cases also responding favourably to novarsenobillon while in 1921 *Da Matta [15] Nogue [16] Broden* and Bernard [10] reported similar

cases Foley and Parrot [17] also in 1920 in reporting 21 cases of juxta articular nodules drew attention to the presence in their cases of syphilitic lesions a history of abortions or of infant mortality and in some the presence of a positive W R In many of the cases mercurial treatment also proved efficacious In the following year these authors [18] recorded a further case showing a partially positive W R

Cange and Argaud [19] also in 1921 in reporting two cases supported the view that the nodules were syphilitic in origin Their first case was that of a woman aged 30 who presented symmetrically placed nodules on the posterior surface of the upper third of both forearms extending downwards from the olecranon They varied in size from a small nut to an apricot and were hard mobile and painless The W R was negative The skin over the area occupied by the nodules showed it is said erythematous papular lesion (? syphilitic) Histologically one of the nodules showed a fibrous tissue growth with giant cells obliterative endarteritis and perivascular infiltration of plasma cells Cange and Argaud s second case [20] was that of an Algerian woman aged 56 who six years previously had acquired syphilis from her husband She developed a chancre on the left labium and later a macular roseola and anal and vulvar condylomata In spite of antisyphilitic treatment ocular symptoms and nodules developed one and a half years later One nodule was present on each elbow the lesions being round very hard and freely movable under the skin

It would appear therefore that there must either be a very close relationship between subcutaneous fibroid syphilomata and many of the cases reported as examples of juxta articular nodules or that in some instances the two conditions have been confused Indeed cases such as Cange and Argaud s first case appear almost identical with the former condition H S Stannus [12] in an admirable review of the relationship of yaws and syphilis states that Gutierrez [21] has done well to call attention to the fact that juxta articular nodules must be differentiated from subcutaneous fibroid syphilomata which closely resemble them but can be distinguished histologically To quote Stannus It appears probable that lack of appreciation of these facts has led many observers to make an incorrect diagnosis and that a diagnosis unsupported by histological examination in the absence of a history above suspicion must remain a doubtful one Both sets of lesions so long as they have not reached an advanced stage of fibrosis respond to treatment by salvarsan

Syphilitic Bursitis

The possibility of relationship between subcutaneous syphilomata and syphilitic lesions in bursae has been considered by Howard Fox The whole subject of bursal syphilis was admirably reviewed in 1909 by Churchman [22] who in a thorough search of the literature was able to collect 26 undoubted cases Of the 26 10 presented somewhat similar features to the cases under discussion and as H Fox points out most of the points on which according to Churchman the diagnosis of bursal syphilis is based might apply to some of the cases of subcutaneous syphilomata – viz history or coexisting signs of syphilis spontaneous development slow evolution symmetrical distribution absence of pain and joint involvement In most cases reported as subcutaneous syphilomata however the situation of the nodules precludes any connexion with bursae and microscopical examination fails to show any tissue resembling that of a bursa

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VI

EPICARDIAL NODULES IN A CASE OF HODGKIN'S DISEASE[1]

H RAST F PARKES WEBER and J G GREENFIELD

The patient P C aged 20 years an apparently normally developed young man was admitted to hospital on June 22 1942 with the history that he had enjoyed good health prior to the war About March 1942 the present trouble commenced to show itself with a kind of symmetrical dermatitis of the face spasms of pain in the thorax sometimes waking the patient up at night spreading around the chest from the vertebral column and also lumbar pains radiating downwards accompanied two or three times by transient retention of urine He had also had sores in the mouth and pustular eruption on the hands (purulent paronychia of one thumb) and body On admission however there was nothing special to be seen except that he still had some dermatitis of the face and eyelids

Blood count (June 24) Hæmoglobin 78 per cent erythrocytes 4 000 000 colour index 0 97 leucocytes 11 800 (polymorphonuclears 73 per cent young forms 3 per cent lymphocytes 17 per cent monocytes 5 per cent eosinophils 2 per cent) Blood sedimentation Much accelerated Blood N P N 25 4 mg per cent Blood cholesterol 160 mg per cent Blood calcium 8 6 mg per cent Total proteins in blood serum 6 48 per cent (albumin 4 54 per cent globulin 1 94 per cent) Fractional tests of stomach contents (July 1) showed moderate hypochlorhydria Nothing special in regard to temperature pulse respiration and urine nor was anything abnormal found by ordinary and X ray examination of the thorax and abdomen No local muscular tenderness such as might suggest myositis Under treatment by liver extract and nicotinic acid there was decided improvement and the pains completely disappeared The patient left the hospital on August 9 1942

He was *readmitted* on November 29 1943 after having had a febrile illness which was thought to be pneumonia and for which he had been treated with sulphapyridine but the treatment had failed to remove the fever the temperature in the evening continuing to rise to 99–101 F A radiogram had suggested bronchopneumonia of the right middle and lower lobes no tubercle bacilli had been found in the sputum A blood count on November 17 had given Hæmoglobin 55 per cent erythrocytes 3 020 000 colour index = 0 9 leuco-

[1]After *Med Press* (194) 214 30

cytes 5 000 (polys 66 per cent lymphos 29 per cent monos 4 per cent eos 1 per cent basos 0)

On readmission the spleen was found decidedly enlarged the lower edge reaching a fingerbreadth or more below the costal margin on inspiration No enlargement of the liver or of the superficial lymphatic glands was noted at first but afterwards there was slight tender enlargement of two subauricular glands on the right side A radiogram of the thorax (November 30) showed some opacity in the right lung and the heart somewhat to the right Electrocardiogram (November 30) Normal The tongue mouth and throat appeared normal Urine Nothing special Blood count Haemoglobin 42 per cent erythrocytes 2 700 000 colour index = 0 95 leucocytes 3,500 one normoblast seen during count of 100 leucocytes Blood culture Negative Two blood transfusions early in December seemed to have some good effect and the patient was treated with anahaemin injection ascorbic acid and riboflavin

In January 1944 the patient was not doing well A skiagram of the thorax (January 3) showed a shadow from the mediastinum into the right lung the whole superior mediastinum was thickened *as in mediastinal Hodgkin s disease* Irregular pyrexia up to 100–101 F in the evening (higher in the later part of January) Blood count (January 10) Haemoglobin 38 per cent erythrocytes 3 030 000 colour index = 0 63 leucocytes 5 100 (polymorphonuclears 57 per cent young forms 2 per cent lymphocytes 20 per cent monocytes 8 per cent eosinophils 8 per cent lymphoblasts 5 per cent) marked aniso poikilocytosis reticulocytes 5 3 per cent Van den Bergh reaction (January 10) Negative direct and weakly positive indirect

The patient s feebleness gradually increased The whole of the right side of the thorax became dull as if from pleural effusion Oedema and ascites supervened The temperature fell somewhat but the pulse and respiration became more frequent there was almost continuous tachycardia and he died on February 25 1944

Necropsy

The superior mediastinum was full of a white lobulated hardish tumour The whole of the right pleura the pericardium and the peritoneum were distended with serous fluid The right lung was completely collapsed and the right parietal pleura was covered with whitish nodules The left lung contained one or more similar nodules of hazelnut size The upper and lower bronchus of the right lung were obstructed by growth connected with the hilum and

mediastinal mass The heart showed numerous nodules of white growth in the epicardium (fig 1) The liver (weight 1 650 grammes) contained one cherry-sized nodule The spleen (350 grammes) con

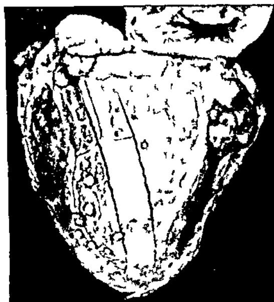


FIG 1—The heart showing epicardial nodules

tained only small nodules The upper pole of the right kidney was infiltrated with a lobular mass of whitish nodules The left kidney showed nothing special Some mesenteric lymph glands were infiltrated There was no thrombosis of the vena cava inferior or iliac veins In regard to superficial lymph glands those in both axillae were somewhat enlarged

Histological Report (By Dr J G Greenfield)

Sections from a piece of the *anterior mediastinum* show a condition of extreme diffuse lymph node fibrosis Only in one or two places are there collections of lymphocytes but a few plasma cells and eosinophil leucocytes are seen in all parts except the most fibrotic There are also numerous large cells with large irregular nuclei or several nuclei The appearances suggest a chronic lymphadenoma (Hodgkin's disease)

In the *kidney* the infiltration is much more typical of Hodgkin's

disease with diffuse reticular overgrowth infiltrated with lymphocytes and numerous eosinophil and Reed (Sternberg) cells

No diffuse infiltration is seen in the *liver* and the small areas of lymphocytic excess in the portal tracts are not abnormal (The single cherry sized nodule in the liver was not examined microscopically)

The growths in the *pericardium* are similar to those in the kidney i e thin fibroblastic tissue infiltrated with lymphocytes and eosinophil leucocytes and containing many large binucleated or multi nucleated (Reed) cells

The *lung* growths are similar but of rather more lax structure and more vascular A few polymorphonuclear leucocytes are present here

In the *splenic nodules* there are still masses of lymphocytes Other wise the growth is more collagenous and there are masses of blood pigment representing the remains of old haemorrhages

Remarks

The skiagram of the thorax taken on January 3 1944 suggested Hodgkin s disease of the mediastinum with pyrexia but a trial of X ray therapy could not be carried out At the post mortem examina tion all the growths presented the characteristic histological appear ance of typical Hodgkin s disease The disease probably commenced in the mediastinum for amongst the patient s early symptoms were spasms of pain in the thorax sometimes waking the patient up at night spreading around the chest from the vertebral column The histological appearances (degree of fibrosis etc) point likewise to the mediastinal mass being of earlier date than the other growths The final multiple involvement of the heart (epicardium) is we believe extremely rare Dr Greenfield sees no reason for calling the case one of Hodgkin sarcoma (Ewing 1922 Weber 1926)

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VII

AN UNUSUAL FINDING BY STERNAL PUNCTURE IN A CASE OF ACUTE ABDOMINAL HODGKIN S DISEASE[1]

F PARKES WEBER and H HUBER

THE patient was a woman aged 46 years with enlargement of liver and spleen who died in the German Hospital London of what we regarded as acute febrile abdominal Hodgkin s disease In the material obtained by sternal puncture Dr Huber found a conglomerate of about 40 cells which were partly syncytial The cells were round with a diameter of about 7 μ Each cell contained a single reticular nucleus of nucleochromatin mostly with one nucleolus The cytoplasm was stained grey blue and was not granular This finding suggested that the case might be one of reticulo-sarcoma or atypical reticulosis

In regard to the post mortem examination we had the help of Dr Bodley Scott and Dr Robb Smith On the whole the case seems to have been one of true Hodgkin s disease rather than one of reticulo sarcoma on the basis of Hodgkin s disease

[1]After *Deut Arch Klin Med* 1939 185 109

VIII

AMYLOIDOSIS ASSOCIATED WITH MYELOMATOSIS
and
Primary Systematized Amyloidosis, especially the type associated with Amyloid Macroglossia (Lubarsch Pick Syndrome)

F PARKES WEBER

THE occasional association of amyloidosis with multiple myeloma (myelomatosis) has been recognized for a long time It was present in the case of *myelomatosis with Bence Jones proteinuria described* by Parkes Weber in 1903 (*Med Chir Trans* London **86,** 395) At the necropsy on that case the tongue was ulcerated and hardened and in microscopical sections stained with methyl violet a good deal of *amyloid or closely allied substance was found* though none was discovered in similarly stained sections of the liver spleen and kidney The rosy coloration with methyl violet showed that the substance in question if it was not actually amyloid was a very closely allied substance *This was doubtless one of the earliest cases of myelomatosis* in which any kind of amyloidosis was detected Since then the pathologist Dr H C Lucey has re-examined some of the material preserved from the original necropsy He found evidence of amyloidosis also about joints but his results have not been published

In the many examples of the association of amyloidosis with myelomatosis referred to by Magnus Levy (*Zeitschr f Klin Med* 1931 **116** 510 and 1933 **126,** 62 and *Acta Med Scand* 1938 **95,** 217) the amyloidosis seems to have been generally atypical that is to say the deposits were mostly nodular and the amyloidosis when systematized did not specially involve the abdominal viscera usually selected in cases formerly regarded as typical amyloidosis Magnus Levy has suggested that both Bence Jones protein and amyloid may be derived from myelomatous bone marrow A remarkable example of generalized nodular amyloidosis combined with myelomatosis and Bence Jones proteinuria in a man aged 35 years was described by *Alice Stewart and Parkes Weber in the Quarterly Journal of Medicine* 1938 New series **7** 224 (Case 4)

PRIMARY SYSTEMATIZED AMYLOIDOSIS AND THE LUBARSCH PICK SYNDROME

A typical case of primary systematized amyloidosis with amyloid macroglossia (Lubarsch Pick Syndrome) without myelomatosis was

described by F Parkes Weber Stanford Cade A W Stott and R J V Pulvertaft in 1937 (*Quart Journ Med* New series 6 181) The patient was a married English woman aged 48 years in whom the correct diagnosis was made by microscopical examination (biopsy) Ten other cases were found in the literature of the subject In one of them (F S Balyeat *California and Western Med* 1935 **43,** 154) according to the published post mortem examination the amyloidosis seems to have been limited to the enlarged tongue For later literature *see* W G Barnard *et al* *Journ Path and Bact* 1938 **47,** 311 and J A Dillon and L R Evans *Ann Intern Med* 1942 **17,** 722 Since 1937 I have myself been shown two further example of the Lubarsch Pick type of primary generalized amyloidosis in men both advanced cases but they have not been published S de Navasquez and H A Treble (*Brain* 1938 **61,** 116) have shown that in primary generalized amyloidosis the nerves may be specially involved I shall not discuss the numerous scattered literature on primary local amyloidoses here In such cases the changes may well be due to a disturbance of local intracellular metabolism For literature on lichen amyloidosis (Freudenthal) and localized amyloidosis of the skin *see* A Dostrovsky and F Sagher *Arch Derm and Syph* 1941 **44** 891

IX

XANTHOMATOSIS HEART DISEASE, ARTERIAL ATHEROMA, GALLSTONES, AND RELATED QUESTIONS[1]

F PARKES WEBER

E Sherwood Jones and P W Robertson (*Brit Med Journ*, 1948 **1**, 1137) draw attention to the question of the relationship of hyper cholesterolaemic xanthomatosis to arterial atheroma Such a relationship was especially discussed by the Russian pathologist S S Chalatow in his German monograph *Die Anisotrope Verfettung* Jena 1922 and in my booklet *Cutaneous Xanthoma and Xanthomatosis* (London 1924 p 14) I illustrated the question by the history of a London surgeon with whom I was acquainted In 1902 at the age of 41 years he had tuberous xanthoma of both elbows About seven years later he began to suffer from intermittent claudication of both lower limbs at first slight but gradually increasing in severity This intermittent claudication continued till his death (from other causes) in 1913 and post mortem examination proved that it was due to severe atheroma (atherosclerosis) of the abdominal aorta and iliac arteries

A striking illustration of the association of xanthomatosis of tendons and tendon sheaths with cardiovascular disease (angina pectoris) in a woman aged 60 years with blood serum cholesterol estimated at 400 mg per 100 ml was demonstrated by H J Anderson in 1943 (*Proc Roy Soc Med* 1943 **36**, 179) Effort angina was first complained of at the age of 52 A sister was known to have had similar nodules and angina of effort

A man with hypercholesterolaemic xanthomatosis told me that a brother of his had recovered from similar lumps on his elbows without medical treatment but I understood that that brother had recently had to have one leg amputated for what seemed to be ischaemic gangrene—very likely connected with atheromatous disease

There may also be a connexion between arterial atheroma and gall bladder stones especially solitary cholesterol stones (D M B Gross *Journ Path and Bact* 1929 **32** 503) This would serve to illustrate the whole subject of the occasional association of different types of local or systemic errors of lipoid (notably cholesterol) metabolism

[1]Enlarged from letters to the *British Medical Journal* 1948 1 1254 and 1948 2 107

Where there is local absence of lymphatic vessels namely in the cornea the cholesterol cells (lipophages) eventually die leaving the cholesterol the cause of arcus senilis (cf I Gordon *Arch Path* 1947 **44**, 247)

Xanthelasma palpebrarum is apparently a regional disorder of cholesterol metabolism – the commonest external cholesterol lesion met with – on the whole more frequent in females and in certain families less frequent in those of purely British ancestry than in those of foreign or partly foreign families Its connexion with other types of xanthomatosis is of course well known and I think that there is often noteworthy frequency of arterial atheroma and gallstones in the same families – probably indicating the not uncommon association of various (local and systemic) errors of cholesterol metabolism

I knew three brothers big men fond of open air exercise especially shooting The eldest of the three a merchant lived in a healthful way largely in the country and died at 72 Towards the end of his life there were aortic and mitral murmurs probably atheromatous and finally he developed enormous cardiac dilatation His younger brother in early middle age had a severe cardiac attack when playing cricket and was found to have aortic regurgitation (I think) possibly due to rupture of an atheromatous valve He died relatively early The youngest of the three brothers an architect died at 70 or 71 apparently of coronary thrombosis He had rather striking xanthelasma palpebrarum and one of his daughters was operated for gallstone A niece (sister s daughter) of these three brothers had slight xanthelasma palpebrarum at about the age of 20 but it had disappeared by 55 and she is now in excellent health at 79 The father of the three brothers died (pneumonia) at 78 and the mother lived to 94 Incidentally this history shows that a family tendency to xanthoma and atheroma does not necessitate early death

The most plausible hypothesis illustrating the relationship of various types of xanthomatosis and atheromatosis is I believe that given so ably by I Gordon Mechanism of Lipophage Deposition in Atherosclerosis *Arch Path* 1947 **44** 247

A very unusual type of xanthomatosis involving the small intestine is described by R Frei (*Schweiz Zeitschr Path Bakt* 1947 **10** 685) His first case was that of a woman who died at 84 of cerebral arteriosclerosis apparently without having shown signs of gastro intestinal disturbance during life At necropsy the small intestine showed yellowish discoloration of the rugae and there was ulcerative colitis Microscopically there was extensive xanthomatosis of the

submucous coat of the small intestine without signs of inflammation and fulminating colitis was present in the large intestine His second case was that of a man aged 43 who died after a sprue like illness of several months duration On microscopical examination large foam cells were seen in the submucosa of the entire gut in addition the mesenteric lymph glands were involved (*see* abstract in *Journ Clin Path* 1948 **1**, 330)

X

ACUTE RAPIDLY FATAL MYELOBLASTIC LEUKAEMIA CLINICALLY RESEMBLING AN ACUTE FEBRILE INFECTION[1]

F PARKES WEBER and E SCHWARZ

The patient (M J K) an unmarried girl aged 20 years who had been engaged on light work in a munition factory was admitted to hospital on June 24 1943 Five days previously she had consulted a doctor on account of faintness and fever For two or three months before that she had been feeling vaguely unwell tired or depressed There was apparently nothing of note in her previous or family history

On admission she was drowsy or semi delirious very anaemic, with fever greatly increased pulse and respiration a crusty sore on the lower lip and two ulcers on the vulva (one on either labium minus) there was no enlargement of any superficial lymph glands and spleen and liver could not be felt though the splenic and hepatic dullness both seemed to be somewhat enlarged There had been apparently some bleeding from the vulva (? connected with the ulcers) just before admission and epistaxis eight or nine days ago At first sight one could think of the possibility of meningococcal septicaemia tuberculous meningitis or even of sepsis from artificial abortion but the finding of a leukaemic blood picture settled the diagnosis though we were at first uncertain whether the condition might not be an acute exacerbation only Treatment did no good (X ray treatment could not be tried but would almost certainly have been absolutely useless) and the patient died four days after admission The fever varied up to 103 2 F pulse mostly about 140 respiration 36 to 60 (shortly before death) A catheter specimen of the urine on admission showed nothing special Blood culture (June 20) negative Radiogram of thorax (June 21) heart large infiltration and opacity at bases of lungs possibly secondary to heart weakness

The blood picture in the hospital – Haemoglobin 24 per cent (fell to 22 per cent) erythrocytes 1 610 000 (fell to 1,240 000) leucocytes 48 300 (fell to 35 000) In regard to the differential count of the white cells the greater portion (about 90 per cent) were non granulated cells evidently of the myeloblast class There were a few monocytes plasma-cells lymphocytes myelocytes and neutrophil polymorphs but of the latter only one or two were seen The red cells showed

[1]After the *Medical Press* 1943 210 190

hypochromia and poikilocytosis No nucleated red cells and no thrombocytes (special staining) were found

Necropsy (June 24 1943) – Ecchymoses of left upper arm chin and lip pericardium pleurae peritoneum pyloric part of intestinal mucosa and of the leptomeninges at the base of the brain The effused blood had penetrated (apparently along vessels) into the actual substance of the brain possibly constituting one cause of the mental state of the patient during the last days of her life The lungs showed (terminal) oedema but no pneumonia or tuberculosis There was no enlargement of the abdominal *or bronchial lymph glands* *The pericardial* ecchymoses were especially in the epicardium and the pericardium contained a little sero-sanguineous fluid Nothing special was noted in the kidneys (rather pale) pancreas adrenals uterus ovaries urinary bladder or stomach The *sternal bone marrow* macroscopically had a somewhat puriform appearance and microscopically when stained by Leishman and Giemsa was found to contain quantities of myeloblasts exactly similar to those found in the peripheral blood during life Marrow from the middle of the shaft of the right femur macroscopically resembled that in the sternum but obviously contained more fat Unfortunately it was not examined microscopically *The spleen* (240 grammes) was somewhat enlarged and of ordinary consistence microscopically Dr J G Greenfield found the splenic pulp very cellular including many plasma cells and a few nucleated red cells no definite myeloblasts or myelocytes could be recognized in it in sections stained with Giemsa *The liver* (1 750 grammes) and gall bladder showed nothing special excepting that macroscopic inspection of the freshly cut surface of the liver showed minute pale rings (rather too distinctly) evidently corresponding to the outer zones of the liver lobules Microscopically Dr J G Greenfield found there were numerous central areas of necrosis in the lobules and in these myeloblasts and myelocytes and nucleated red cells were seen In looking at the sections it seemed to one of us (F P W) that the centro lobular change was analogous to the centro lobular atrophy in nutmeg liver the dilated blood vessels in the centres of the lobules in the present case being crammed with the leukaemic blood The cardiac weakness and pulmonary oedema during life might well have had a causal relation to this centro lobular atrophy which might almost be termed acute nutmeg liver

We have to thank Dr F P Duras for his help in the post mortem examination and Dr J G Greenfield for the microscopical examination of the liver and spleen

Remarks

Clinically as in most cases of acute leukaemia there was some resemblance to an acute febrile infection and indeed cases of this kind do suggest that human leukaemia (like fowl leukaemia) may ultimately be proved to be of infective nature The absence of specific leukaemic interlobular infiltration in the liver (on microscopic examination after death) shows that the case was really acute and not merely one of acute exacerbation of chronic myeloid leukaemia The great shock of the commencing disease on the bone marrow probably accounted for the extreme anaemia and the absence of nucleated red cells in the peripheral blood as well as perhaps for the absence of thrombocytes The absence of thrombocytes may well have been a main cause of the haemorrhagic features of the case

XI

LEUKANAEMIA AND MYELOSCLEROSIS[1]

F PARKES WEBER

I WISH to enter a plea for the retention of the term leukanaemia in regard to cases of what is now termed leuco-erythroblastic anaemia with clinical or post mortem evidence that a greatly damaged haemopoietic activity of the bone marrow has been supplemented by extramedullary *haemopoiesis in the spleen and probably liver* (megakaryocytic splenomegaly and megakaryocytic hepatomegaly) and possibly in lymph glands It will however be convenient to exclude those cases in which the failure of medullary haemopoiesis is due to carcinomatous infiltration or other neoplastic destruction of the bone marrow The term leukanaemia would then be restricted to cases in which the bone marrow failure is due to myelophthisis or *fibrotic change (myelofibrosis if this hybrid name is permissible)* or to any kind of myelosclerosis in which the bone marrow is gradually destroyed or replaced by non neoplastic endosteal osteoid or osseous formation The term myelo-osteosclerosis would distinguish such cases of *bony* myelosclerosis from myelofibrosis

A typical example of leukanaemia in the sense in which I propose to retain the term was that which I described in 1904 under the *heading A Case of Leukanaemia with Great Hyperplasia of the* Spleen and Prevertebral Haemolymph Glands and with Increase of Connective Tissue in the Bone marrow (*British Medical Journal* 1904 **1**, 1416 and *Trans Path Soc Lond* 1904 **55**, 288) The patient was a man aged 58 years admitted to hospital suffering from great anaemia progressive weakness anorexia and tinnitus These symptoms had developed during the last twelve months in fact he *had apparently been able to insure his life about one year* before admission He had lived in England since 1865 and had never had malaria or been out of Europe Together with the leuco-erythroblastic anaemia there was great enlargement of the spleen and liver At the necropsy the marrow of the shaft of the left humerus was carefully examined and found to have undergone *transformation into a* red substance of unusually firm consistence This myelofibrosis was confirmed by microscopical examination In sections of the spleen liver and kidneys there was absence of any reaction for free iron such as is found in pernicious anaemia I concluded It is very tempting to suggest that the spleen (haemal gland) and the prevertebral

[1]Letter reprinted from *British Medical Journal* 1947 2 1057

haemolymph glands were actively engaged in supplementing the erythrocyte forming functions of the diseased bone marrow I alluded also to what French authors (as Vaquez and Aubertin) termed anemie splenique myeloide In a later paper (*Med Pr* 1928 **176,** 174) I recorded another report by Sir J C G Ledingham who kindly made a microscopical examination of the organs from my case after *the one which I had reported He drew attention to the peculiar* type of myeloid transformation in the liver There were he said numerous areas of veritable marrow with extraordinary numbers of megakaryocytes which occasionally showed mitosis Some of the megakaryocytes were so large that they would not possibly have passed through the fine interacinous capillaries

I borrowed the term leukanaemia from W von Leube and from Arneth s haematological account of von Leube s case (*Dtsch Arch klin Med* 1901 **69,** 331) and H Luce s paper (*Ibid* 1903 **77** 215) though my case was not exactly similar I suppose now that my case must be classified among the cases of myelofibrosis of uncertain aetiology with resulting symptomatic leuco-erythroblastic anaemia G Carpenter and C M Flory (*Arch intern Med* 1941 **67,** 489) have headed a recent paper Chronic Non leukaemic Myelosis Report of a Case with Megakaryocytic Myeloid Splenomegaly Leuco erythro blastic Anaemia Generalized Osteosclerosis and Myelofibrosis As explained by L A Erf and P A Herbert (*Ann intern Med* 1944 **21,** 863) myelofibrosis is not of course synonymous with aplastic anaemia The bone marrow in the former is fibrotic and in the latter it is fatty Extramedullary haemopoiesis exists in the former but not in the latter

An important clinical point is that in leukanaemia as I propose to limit the term splenectomy is as has been often pointed out absolutely contra indicated because the enlarged spleen (part of the con servative mechanism of extramedullary haemopoiesis) is helping to keep the patient alive

Incidentally I should like to know whether the condition of polyostotic focal fibrous dysplasia (in which I would include cases of Albright s disease) ever leads to a condition of leuco-erythroblastic anaemia in fact to leukanaemia in the restricted sense of the term which I advocate Another question Can there be gelatinous degeneration of bone marrow such as is occasionally met with at post mortem examinations which is not merely a *paulo-ante mortem* phenomenon but may allow the patient to live long enough to develop a resulting condition of myelofibrosis?

XII

CEREBELLO OLIVARY DEGENERATION AN EXAMPLE WITH HEREDO FAMILIAL INCIDENCE[1]

F PARKES WEBER and J G GREENFIELD

AMONGST examples of familial developmental abiotrophy of the nervous system are many family groups in which probably no histological examination has ever been made for instance some of those in which tremor commencing after adult age slowly increases and ultimately tends to take on an intention character and in which the affected members live long and in some respects clinically resemble cases described as hereditary ataxia In regard to collected literature and discussions on cerebellar degeneration and hereditary ataxia we must refer to Hassin and Harris (1936) and to the monograph on Hereditary Ataxia by Julia Bell and E A Carmichael (1939)

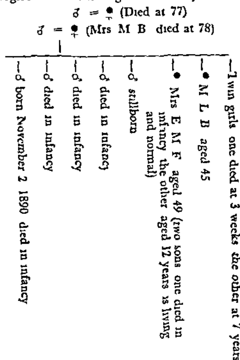
The record given here is of the case of a woman with hereditary cerebello-olivary degeneration in whom the disease commenced with unsteadiness of gait at 60 years of age She died at 78 and the result of the post mortem examination is described Her mother died at 77 and evidently suffered from the same disease which first showed itself at 60 in the same way by unsteadiness of gait The only children of the patient who lived beyond childhood two daughters aged 45 and 49 respectively have been clinically examined and are found to be suffering from a mild degree of the same disease which in both of them commenced at the age of 40 with unsteadiness of gait

Case Report (F Parkes Weber)

Mrs M B aged 78 was admitted to hospital on August 14 1941 with the following history About the age of 60 she began to suffer from unsteadiness of gait and weakness in legs with some slurring of speech These symptoms gradually increased but she continued to be able to get about a little with the aid of a stick though of late she had not been able to extend her legs completely There was obviously a condition of progressive dementia and for the last twelve months she had hardly been able to keep awake Her sight and hearing had been failing and of late there had been incontinence of urine and faeces She was still able to some extent to answer questions The patient was also suffering from recurrent attacks of a kind of senile pruriginous purpuric eruption almost limited to the left fore arm

[1]From *Brain* 1942 65 220

Genealogical Table showing the Heredity of the Disease



and hand though there was itching and scratching of other parts also

In the hospital —By ordinary and X ray examination the heart was enlarged to the left and there were calcified plaques in the aortic arch Calcified plaques were also visible in the abdominal aorta and in the region of the coeliac axis No enlargement of the liver spleen or superficial lymphatic glands Considerable scoliosis Marked decalcification of vertebrae Calcification of costal cartilages Thickening of the cranial vault Pituitary fossa apparently normal Brachial blood pressure 220/80 mm Hg Blood-count Haemoglobin 62 per cent erythrocytes 3 250 000 colour index = 1 0 leucocytes 5 500 (polymorphonuclears 71 per cent lymphocytes 25 per cent monocytes 1 per cent eosinophils 3 per cent) Thrombocyte-count 320 000 to 400 000 per c mm of blood Blood sedimentation accelerated first hour 42 two hours 83 Blood Wassermann and Kahn reactions negative Urine specific gravity 1 017 acid trace of albumin no sugar some leucocytes but no tube-casts were found in the centrifuged

sediment Eyes and pupils (Dr C Markus) Nothing abnormal excepting slight incipient cataract both sides No spontaneous nystagmus (at rest) Patellar and ankle reflexes active on both sides Superficial abdominal reflexes not obtained Plantar reflexes flexor on right side doubtful on left side Sensation no evidence any where of anaesthesia or hyperaesthesia excepting tenderness in con nexion with passive movements of the flexed lower extremities

The patient seemed always to be apathetic and drowsy lying in bed with her legs drawn up The upper limbs were relatively little affected There was general emaciation but no obvious localized mus cular atrophy anywhere She scratched herself very much The intermittent pruriginous purpuric (ecchymotic) eruption in the left upper limb continued and it is doubtful whether treatment by vitamin C did any good The general condition further deteriorated Bed sores developed During the last few days she seemed to be hardly conscious and did not even scratch herself any more She died on November 3 1941

Family history – The patient's mother had suffered from similar symptoms which began at 60 years of age with unsteadiness of gait She gradually lost the use of her legs and arms and control of her sphincters Mental degeneration was complete before her death at 77 The patient (Mrs M B) had 9 children 5 boys and 4 girls One of the boys was stillborn and the others died in infancy Of the four daughters two were twins one of whom died at 3 weeks and the other at 7 years The remaining two daughters are living aged 45 and 49 respectively and both of them at 40 commenced to show slight unsteadiness of gait as their mother did at 60 There is no history of in breeding in the family The patient (Mrs M B) and her husband were not blood relatives nor were her mother and father Both the daughters have been examined

The younger of the two sisters Miss M L B aged 45 who is still able to do her work as a domestic servant says that she has always had some slight difficulty in walking but that her real trouble com menced at 40 with unsteadiness of gait At present she has a slightly staggering and stiff gait on a somewhat too broad base slight deficiency of facial mobility (Parkinsonian like) slight slurring of speech and slight intention tremor in the left hand No definite mus cular ataxia by ordinary tests No Rombergism No nystagmus or anything abnormal in the eyes Nothing abnormal in regard to nervous reflexes and sensation Nothing abnormal in regard to examination of the thorax abdomen and urine excepting that a

radiogram shows that the bronchial markings are somewhat increased at the right base Brachial blood pressure 125/90 mm Hg Menstruation still regular Blood Wassermann reaction negative She likes her employment and feels better when she is working but her employers are careful not to overwork her

The elder of the two sisters Mrs E M F aged 49 married at 30 and has had two children (both boys – one died soon after birth – the other is now 12 years old and has always been apparently bodily and mentally normal) Menopause at 46 She walks fast and easily but somewhat unsteadily and on too broad a basis This unsteadiness of gait was first noted at 40 – the same age as that at which her sister s abnormality of gait was first noted She is apparently able to live an ordinary normal life In regard to speech there is some definite slurring at least in certain words No definite muscular ataxia by ordinary tests Nervous reflexes normal Nothing abnormal in regard to the eyes excepting hypermetropia No deafness No tremor No nystagmus No definite stiffness of face Sensation apparently normal Nothing abnormal in regard to thoracic and abdominal viscera and urine Brachial blood pressure 145/80 mm Hg Blood Wassermann and Kahn reactions negative

Clinical Diagnosis

It seemed obvious that the heredo-familial nervous disease was a developmental abiotrophy of some kind but one was inclined to the diagnosis of a presenile encephalopathy possibly of the Creutzfeldt Jakob type The extreme degree of general arterio clerosis however made me doubtful Dr Greenfield s post mortem histological examination has finally decided in favour of parenchymatous cerebellar atrophy together with extreme generalized arteriosclerotic changes Thanks are due to Dr H C Lauber and Dr K Blum in regard to the clinical examination of the case

Post mortem examination – Emaciated body with legs bent up and decubitus Extreme calcareous atherosclerosis of the thoracic and abdominal aorta and branches some of the mesenteric arteries superficially resembled thick firm india rubber tubing The heart (weight 250 grammes) showed relative hypertrophy of the left ventricle and some atheroma of the aortic valve The right and left kidneys (75 and 100 grammes respectively) showed nephrosclerosis with adherent capsules and little cysts The liver (875 grammes) and spleen (100 grammes) showed nothing special macroscopically nor was anything abnormal noted in the other abdominal organs (not all were

examined) and lungs The calvarium was sclerosed Brain (880 grammes) cerebral convolutions appeared shrivelled with excess of cerebrospinal fluid in the leptomeninges Pituitary gland macroscopically not abnormal Much calcification of the arteries at the base of the brain

The brain and whole spinal cord together with pieces of some of the other organs were sent to Dr Greenfield for histological examination

Histological Report and Discussion

J G GREENFIELD

Microscopical examination of the viscera and muscles —All the viscera were the seat of severe arteriosclerotic changes These were most obvious in the kidneys where the walls of many of the medium sized arteries were so greatly thickened in a concentric manner that the lumen was almost completely obstructed Many of the glomeruli were completely sclerosed and there were localized superficial areas of fibrosis with some small celled infiltration and degeneration of the tubular epithelium Elsewhere there was a tendency to dilatation of the convoluted tubules The glomerular arterioles showed only a moderate degree of hyaline degeneration

In the spleen also there was great concentric thickening of the vessel walls and some hyaline degeneration in the small vessels in the Malpighian bodies

The liver showed little abnormality except moderate fatty degeneration

The muscles examined showed a very severe degree of simple atrophy affecting a large proportion of the fibres In these fibres the sarcolemmal nuclei appeared more numerous than normal and the fibres were only 5 to 10 μ in width but they retained their cross striation There was widespread increase of fibrous tissue These changes are in keeping with disuse atrophy but may have been contributed to by poor vascular supply

Examination of the brain and spinal cord —The brain and cerebellum were small but no disproportionate shrinkage of the cerebellum was obvious The sulci of the brain were wide as in many senile brains On section of the brain small brownish areas with cavitation in their central parts were seen in the anterior part of the corpus striatum on the left side and in the upper and anterior part of the thalamus on the right side The vessels in the putamen were

abnormally prominent and were surrounded by a narrow zone of brownish discoloration Apart from these areas in the basal ganglia no softenings or discolorations were visible macroscopically in the central nervous system

Microscopically the large areas visible to the naked eye showed rarefaction of the tissues with the formation of small lacunae There was throughout these areas loss of nerve cells and fairly dense neuroglial sclerosis and they were full of pigments which stained with Prussian blue Some smaller foci of neuroglial scarring with deposition of blood pigment were also seen The narrow zone round the vessels showed only absence of nuclei and rarefaction of the tissues No other definite abnormality was seen in the basal ganglia In the cortex the nerve cells contained some excess of lipochrome pigment but there were no areas of paling and no senile plaques were found The vessels throughout the brain were rather thick walled and those in relation to the larger scars in the basal ganglia had their lumen partially obstructed by atheroma These changes were all clearly of vascular origin In the mid brain and pons also small foci of ischaemic degeneration were found in the anterior part of the red nucleus on one side there was a dilated and thrombosed vessel round

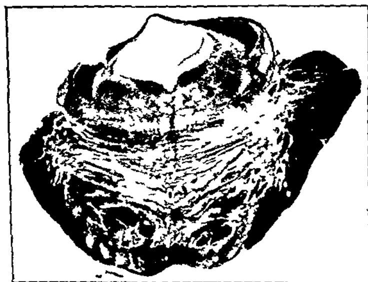


Fig 1—Transverse section of pons showing ischaemic area in ventral part on one side and another involving the mesial fillet on the opposite side Loyez myelin stain.

which there was some loss of nerve cells and deposition of blood pigment In the opposite nucleus ruber there were narrow zones round the vessels in which the myelin stained poorly Numerous areas of ischaemic degeneration were seen in the ventral part of the pons These were most apparent in sections stained by Lovez myelin method counterstained with carmine They appeared as areas of pallor or loss of myelin staining following the course of a vessel through the ventral half of the pons chiefly in its deeper parts At about the mid level of the pons a small area of loss of tissue was present in the centre of the ventral half on one side and another in the outer part of the mesial fillet on the opposite side (fig 1) The latter had caused Wallerian degeneration of this part of the fillet at higher levels When examined by Loyez stain it was clear that these areas were of vascular origin and were not due to systemic degeneration of neurons In many areas in the pontine nuclei the nerve cells at one side of a group had disappeared their place being taken by small round nuclei the remainder of the neurons in this group were usually normal Pallor of myelin staining was not obvious along the line of transverse fibres arising in groups of neurons which had disappeared but affected both transversely and vertically coursing fibres along the line of a vessel Both in the affected groups of nerve cells and in the areas of myelin degeneration there was fairly dense neuroglial scarring with the presence of many large astrocytes with thick processes The great majority of the neurons of the nuclei pontis were perfectly normal and the transverse fibres and middle peduncle stained darkly There was however some shrinkage of the ventral half of the pons Except for the lesion in the region of the fillet the tegmentum pontis was normal

Cerebellum —On section of the cerebellum in the sagittal plane there was an obvious disproportion between the size and width of the folia on the upper surface which were shrunken and those of the tonsils flocculus and the anterior part of the inferior vermis which appeared to be fairly normal This was still more obvious in large sections in this plane in which the granular layer of the tonsils was much wider than that in other parts of the cortex (fig 2) The shrinkage was everywhere greatest in the anterior part of the superior cortex and was rather greater here in the vermis than in the lateral lobes As one passed backwards and round to the inferior cortex there was a gradual increase in the width of the layer But except for the tonsils and flocculus no part appeared to be of normal thickness Under low microscopical powers the molecular layer also was seen to

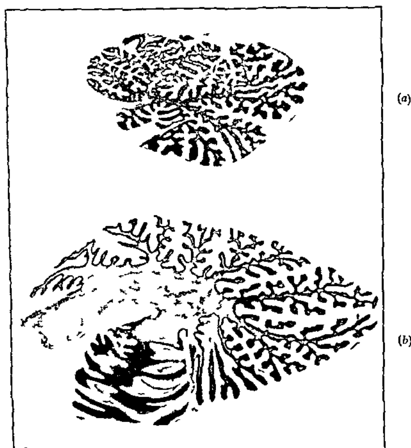


Fig 2—Sagittal sections through (*a*) the vermis and (*b*) the lateral lobe of the cerebellum showing atrophy of folia on the superior surface Iron haematoxylin van Gieson

be shrunken proportionately to the granular layer and to be somewhat rarefied Much greater however than the shrinkage of these layers of the cortex was the disappearance of Purkinje cells Only an occasional shrunken cell could be seen in the most affected parts of the cortex such as the anterior superior parts of the vermis (lobulus centralis) and elsewhere they were so sparse that it was easy to find folia containing none Most of the Purkinje cells seen were shrunken and stained poorly again with the exception of those in the tonsils and flocculus most of which stained normally Even in these lobules the Purkinje cells appeared to be rather reduced in number and many

were shrunken but neither change was of greater degree than is found in many senile arteriosclerotic brains Except in the most affected folia the basket fibres were fairly well preserved and in sections stained by the Gros Bielschowsky method these fibres stood out prominently (fig 3) Torpedo like swellings on the axons of the



FIG 3—Cerebellar folia showing loss of Purkinje cells with preservation of basket fibres The granule cells in this region are rather more sparse than normal Gros Bielschowsky—alum carmine

Purkinje cells were fairly numerous in folia which were moderately affected None were seen in folia from which almost all the Purkinje cells had disappeared and nowhere could more than one be found in a higher power field The myelinated fibres which lie in the layer of Purkinje cells were as well stained in the most affected folia as in the least affected In the more affected folia the granular layer was thinner and its cells sparser than normal and a layer of Bergmann cells lay in the Purkinje cell layer slightly separated from the granular layer Gliosis in both molecular layer and white centre was proportional to the degree of degeneration and was everywhere isomorphic *The white centres showed a varying loss of fibres never very severe* No fat was found in sections stained by Scharlach R The dentate nucleus and roof nuclei appeared perfectly normal and the superior cerebellar peduncle stained well

Medulla —Unfortunately the medulla had been cut off short in removing the brain and only the upper end was available for section

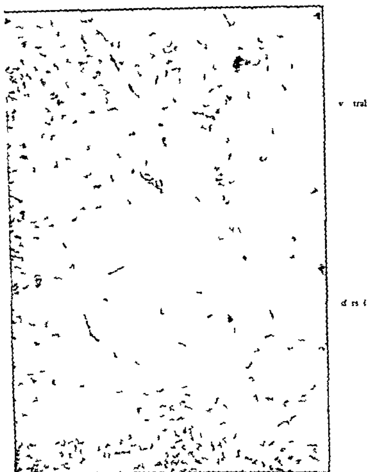


FIG 4—Low power view of inferior olives at upper end of medulla showing great loss of nerve cells especially in dorso medial part (Lower right hand area indicated by arrow) Nissl—toluidin blue

Here at the junction of the pyramid and inferior olive on one side there was a thrombosed vessel surrounded by considerable deposition of blood pigment and slight pallor in the staining of the myelin sheaths There was at this level obvious shrinkage of the ventral part of the medulla and narrowing of its antero-posterior diameter The inferior olives looked smaller than normal but projected to some extent on the surface

Microscopically there was a striking difference between the condi

in those of Akelaitis in all of which the cortex on the superior surface of the cerebellum was especially degenerated the greatest degeneration of the olives was found in their dorsal folds This is in agreement with the work of Holmes and Grainger Stewart (1908) who examined the cells of the inferior olives for retrograde chromatolysis after acute and sub acute partial lesions of the cerebellar cortex and found that the dorsal half of the olives corresponded to the superior surface of the cerebellum In Kufs case also there was a similar special incidence of the degeneration on the dorsal half of the olives He does not give details of the localization of the cerebellar degeneration On the other hand in Schob s case of primary cortical cerebellar degeneration the ventral and dorsolateral parts of the olives were most degenerated He does not state what parts of the cerebellar cortex were specially affected except that the neo-cerebellum was more affected than the palaeo cerebellum and the lateral lobes more than the vermis He considered however that the degeneration of the olives was secondary to that in the cerebellar cortex – a retrograde degeneration Gordon Holmes pointed out that a long standing interruption of physiological function might lead to degeneration of neurons even though their axons were not directly involved in the degeneration It is on this basis that we can most easily interpret the olivary degeneration as secondary or retrograde seeing that according to modern teaching the termination of the olivary axons is as mossy fibres round the dendrites of the granular cells and in our case at least the granule cells were relatively little affected However the degree of degeneration may have been sufficient to lead to retrograde degeneration of such labile neurons as those of the inferior olive

If the olivary degeneration be considered as secondary to th degeneration of the cerebellar cortex it would appear that the term cerebello olivary would describe the degeneration better than olivo-cerebellar which suggests at least that the degeneration of the olives was of equal importance to that in the cerebellar cortex There appears to be little in common between such cases of cerebello fugal degeneration and the cerebello-petal disease *olivo-ponto cerebellar* atrophy in which the degeneration is usually much greater in the olives and pontine nuclei and their axons than in the cerebellar cortex In fact the latter may be entirely spared

We therefor[illegible] our case as a familial instance of cerebello olivary dege[illegible] with those of Gordon Holmes and Akelaitis a[illegible] and Harris as including cases of

this kind in the group of olivo-ponto-cerebellar atrophy Only the examination of more familial cases of this nature can establish the justice of this position but in the present state of our knowledge it appears to be logical

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XIII

ENCEPHALOPATHIA ARTERIOLOSCLEROTICA BASALIS LETHARGICA[1]

F PARKES WEBER and K BLUM

SOMNOLENCE or lethargy from brain disease when it occurs as a main symptom without gross compression (large tumours abscesses haemorrhages internal hydrocephalus) is often associated with paralysis of eye muscles and ptosis This favours the view that the oculomotor nerve nuclei are intimately connected with the sleep centre as Mauthner suggested in 1890 A striking example of this association is the encephalopathia first described by Wernicke in 1881 and named by him polioencephalitis acuta haemorrhagica superior this condition is now supposed to be due to deficiency of vitamin B and to various toxic and other conditions (Campbell and Biggart 1939) Owing to the predominance of lethargy in the clinical picture Economo named the epidemic encephalitis which he described in 1917 encephalitis lethargica The encephalopathy in our case clinically so closely resembled encephalitis lethargica that it might be called pseudo encephalitis lethargica but we suggest that a more suitable term is encephalopathia arteriolosclerotica basalis lethargica

Case History

A married Englishwoman aged 63 was admitted unconscious on February 6 1941 having collapsed in the street after ailing for a few days with headache and tiredness According to her daughter he had been knocked about in an Anderson shelter during two or three air raids in September 1940 Otherwise there was nothing special in her past history She had occasionally taken alcohol in moderation In the hospital she was somewhat restless somnolent breathing normally She was small and thin and her skin was somewhat atrophic Temperature 97 F pulse rate 72 Brachial blood pressure 135/85 mm Hg Nothing abnormal on examination of heart lungs and abdomen no enlargement of liver or spleen Pupils unequal right larger than left the left reacted well the right sluggishly Knee jerks present on both sides No plantar reflex obtained Some cutaneous hyperaesthesia Urine specific gravity 1024 acid trace of albumin no sugar a few leucocytes and calcium oxalate crystals in the centrifuged deposit Blood Wassermann reaction negative

[1]From the *Lancet* 1942 1 503

Blood count on February 18 red cells 6 100 000 Hb 110 per cent colour index 0 9 white cells 6 800 polymorphs 69 per cent lymphocytes 21 per cent monocytes 4 per cent eosinophils 6 per cent

On February 20 she was still lethargic but she could sometimes be roused to answer questions and could be fed with a spoon though insufficiently The temperature and respiration were normal though during the first week in hospital the temperature had been slightly raised (never above 101 4° F) and the pulse rate somewhat rapid There was slight but definite ptosis on the right side The right eye appeared to diverge slightly to the right as if from paresis of the internal rectus oculi Ophthalmoscopy by Dr Charles Markus revealed nothing abnormal in either fundus there was no cataract Lumbar puncture was impossible owing to kyphoscoliosis

The lethargy deepened and early in March no answer could be obtained to questions She could not take food The ptosis on the right side increased the right pupil was larger and reacted sluggishly and afterwards not at all whereas the left pupil reacted promptly to light Treatment was by hexamine-caffein injections and (on account of the dehydration) by subcutaneous infusions of hypertonic saline On March 8 the temperature in the morning was 104 F and there were pneumonic signs on the left side breathing was difficult She died at midday

Post mortem examination of the head only was permitted The brain weighed 1265 grammes its surface was very congested there was no internal hydrocephalus The pituitary gland appeared macroscopically normal Dr J G Greenfield gave the following report on the brain Macroscopically a small haemorrhage with surrounding softening is seen in the centre of the right optic thalamus Microscopically this softening extends outwards between the red nucleus and the superior nucleus of the thalamus from the wall of the ventricle for about two-thirds of the width of the thalamus There are also several small old softenings in the right lenticular nucleus On the left side there is a smaller focus of softening on the ventricular surface of the thalamus just in front of the posterior commissure This is not visible macroscopically It forms a semicircular area about 1 cm long in the antero-posterior direction extending about 6 mm outwards into the thalamus No other foci of softening found The cortex in all areas examined the brain stem and cerebellum are microscopically normal except for vascular congestion

Dr Greenfield on examination of his sections again wrote that he thought there was enough thickening of the small arterioles to

account for the softenings that were present There was no softening or other abnormality round the aqueduct in the upper end of the mid brain nor was there any evidence of capillary and endothelial hyper plasia such as one sees in Wernicke s encephalopathy He added I should therefore class the case as one of cerebral arterial disease of unusual localization

Discussion

The predominant symptoms of the case – lethargy oculomotor palsy with ptosis – resembled those of acute encephalitis lethargica but the post mortem findings show that these symptoms were really due to an arteriolosclerotic change in the basal ganglia of the brain with resulting areas of ischaemia and haemorrhage There was nothing to suggest a toxic or infectious aetiology blood diseases trauma carbon monoxide poisoning alcoholism and burns could be excluded As Dr Greenfield pointed out there was no softening or other abnor mality round the aqueduct in the upper part of the mid brain no was there any evidence of capillary and endothelial hyperplasia such as is met with in Wernicke s encephalopathia For our case and similar ones we think we are justified in suggesting the use of the term Encephalopathia arteriolosclerotica basalis lethargica It is a purely descriptive term taken partly from the morbid histology and partly from the clinical aspect of the disease If preferred instead of the clinical epithet lethargica the pathological epithets ischaemica et microhaemorrhagica might be substituted

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XIV

ACUTE PULMONARY OEDEMA WITH HYPOGLYCAEMIC COMA

An Example of Acute Pulmonary Oedema of Nervous Origin[1]

F PARKES WEBER and K BLUM

The patient a man (A N) aged 40 years was receiving 60 units of protamin zinc insulin daily for his diabetes mellitus when he was infected with influenza As a result he fell into a sub comatous condition but he recovered quickly with daily 90 units of ordinary insulin and 100 grammes of carbohydrate (porridge) the urine becoming free from sugar and ketone bodies in three days About a week later on February 1 1942 at 6 p m after an injection of 30 units of ordinary insulin the patient complained of a disagreeable feeling of hunger which was got rid of by 20 c c of a 20 per cent solution of glucose together with a meal of porridge Six hours after the insulin injection the patient during apparently ordinary sleep fell into a condition of coma which commenced with typical pulmonary oedema There were the severest symptoms of hypoglycaemic shock unconsciousness extremely contracted pupils which did not react to light muscular rigidity restlessness ankle and patellar clonus bilateral plantar reflex of Babinski type psychotic screaming One might describe the condition as one of screaming coma with tetanus like rigidity of limbs and trunk (opisthotonus) Treatment for the hypoglycaemic coma did not remove the pulmonary oedema but a hyoscine atropine injection worked immediately and brought the severe attack to an end though the patient seemed rather weak for two or three days afterwards

Discussion

In the present case there was no evidence of mitral stenosis coronary sclerosis myocardial inadequacy arterial hypertension or any chronic disease of the lungs or cardio vascular system and it seems clear that the acute pulmonary oedema must have been of nervous origin We would compare it to the attacks of pulmonary oedema sometimes associated with epileptic attacks and occasionally constituting the fatal termination In rare cases of paroxysmal pulmonary oedema (Riesman 1907 Case 2) cerebral symptoms such as fleeting aphasia paralysis of limbs stupor or coma have been associated with the

[1]From the *Journal of Neurology and Psychiatry* 1942 5 34

attacks Shanahan (1908) recorded a number of cases illustrating acute pulmonary oedema as a serious complication of epileptic seizures and Ohlmacher (1910) described five epileptic cases in which acute pulmonary oedema constituted the terminal event Langeron (1925) discussed the case of a woman in whom epileptic crises were regularly followed by an attack of acute pulmonary oedema One of us (Weber 1922) would also compare as an analogous phenomenon eclamptic attacks in children during which auscultation of the chest reveals rapid filling up with coarse moist rales passing away when the attack subsides Such temporary bronchorrhoea in children during eclamptic states is probably due to irritation of the broncho-secretory fibres of the vagus nerve Moutier (1918) has drawn attention to occasional cases of fatal pulmonary oedema in soldiers suffering from cerebral wounds and the possible danger of adrenalin injections in such cases Aubertin (1906) experimentally in animals produced convulsions and acute pulmonary oedema by lead poisoning Bezançon and others (1932) recorded the case of a woman aged 39 years with post encephalitic Parkinsonism without any cardiac aortic or renal lesion who suffered from recurrent attacks of acute pulmonary oedema one of which proved fatal Porter and Greenfield (1941) at a Meeting of the Neurological Section of the Royal Society of Medicine communicated a case of the Arnold Chiari malformation of the brain stem with a fatal termination resembling acute pulmonary oedema It was suggested that the clinical picture was produced by an excessive secretion of the bronchial mucosa glands (? a central autonomic phenomenon) and that the response to atropine was in favour of that view

Langeron (1925) in the account of his case above referred to regarded the attacks of acute pulmonary oedema in that case as a visceral manifestation of epilepsy He stated that this sympathetic epilepsy with visceral manifestations was from his point of view a spreading out (extension) of the cortical epilepsy with muscular motor manifestations

Manunza (1935) has drawn up an elaborate classification of pulmonary oedema of nervous origin His first class comprises those cases connected with cerebral affections (inflammations haemorrhages tumours epilepsy) whilst he makes a second class of the cases associated with medullary affections (myelitis haematomyelia tabes dorsalis) and a third class with affections of the vegetative nervous system and dysneurotonic states his fourth class consists of cases of traumatic nervous origin Here one might mention that

Muller (1891) described an attack of acute pulmonary oedema associated with angioneurotic oedema of the face

It is certain that the origin of attacks of acute pulmonary oedema varies considerably in different cases and that in most cases multiple factors are at work but it must be admitted that in some cases an attack may arise in the absence of any true weakness of the right side of the heart (as judged from ordinary and X ray and electrocardiographic examination) and without any sudden congestion of the pulmonary blood vessels due only to reflex or other disturbance of nervous centres Hess (1931 1932 1933 1939) lays stress on the probable intervention of nervous reflexes Impulses he thinks which arise sometimes but not always in the heart irritate the vasodilators of the lungs and produce active congestion together with increased transudation into the pulmonary alveoli In this process according to his views the vagus nerve plays an important part Wassermann s observation (1933) is interesting namely that in some cases pressure on the vagus fibres in the carotid (carotid sinus) can suppress the development of an attack—as it may likewise suppress some attacks of acute paroxysmal tachycardia Certain observations in experimental pharmacology speak in favour of a vagal causative mechanism in acute pulmonary oedema vagus irritation from cholines and acetylcholine (Dale 1914) vagotropic effect of pilocarpin with provocation of an attack of pulmonary oedema the effect of Sympatol during an attack in diminishing vagotonus through excitation of sympathetic fibres

We suggest that in our case the attack of acute pulmonary oedema was of pure central nervous origin due to cerebral oedema and irritation of the vagal nervous system The clinical symptoms and the rapid response to hyoscine and atropine support this view

Summary

A case is described of acute pulmonary oedema combined with hypoglycaemic coma as analogous to the cases connected with epilepsy and other cerebral disturbances Various nervous origins of attacks of acute pulmonary oedema are shortly considered

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Dale Sir H H (1914) *J Physiol* (P) 48 iii

attacks Shanahan (1908) recorded a number of cases illustrating acute pulmonary oedema as a serious complication of epileptic seizures and Ohlmacher (1910) *described five epileptic cases in which* acute pulmonary oedema constituted the terminal event Langeron (1925) discussed the case of a woman in whom epileptic crises were *regularly followed by an attack* of acute pulmonary oedema One of us (Weber 1922) would also compare as an analogous phenomenon eclamptic attacks in children during which auscultation of the chest *reveals rapid filling* up with coarse moist rales passing away when the attack subsides Such temporary bronchorrhoea in children during eclamptic states is probably due to irritation of the broncho secretory fibres of the vagus nerve Moutier (1918) has drawn atten tion to occasional cases of fatal pulmonary oedema in soldiers suffering from cerebral wounds and the possible danger of adrenalin injections in such cases Aubertin (1908) experimentally in animals produced convulsions and acute pulmonary oedema by lead poison ing Bezançon and others (1932) recorded the case of a woman aged 39 years with post-encephalitic Parkinsonism without any cardiac aortic or renal lesion who suffered from recurrent attacks of acute pulmonary oedema one of which *proved fatal* Porter and Greenfield (1941) at a Meeting of the Neurological Section of the Royal Society of Medicine communicated a case of the Arnold Chiari *malformation of the brain stem with a fatal termination resembling* acute pulmonary oedema It was suggested that the clinical picture was produced by an excessive secretion of the bronchial mucosa *glands (? a central autonomic phenomenon) and that the response* to atropine was in favour of that view

Langeron (1925) in the account of his case above referred to *regarded the attacks of acute pulmonary oedema in that case as a* visceral manifestation of epilepsy He stated that this sympathetic epilepsy with visceral manifestations was from his point of view a spreading out (extension) of the *cortical epilepsy with muscular* motor manifestations

Manunza (1935) has drawn up an elaborate classification of pulmonary oedema of nervous origin *His first class comprises those* cases connected with cerebral affections (inflammations haemo-rrhages tumours epilepsy) whilst he makes a second class of the cases associated with medullary affections *(myelitis haematomyelia* tabes dorsalis) and a third class with affections of the vegetative nervous system and dysneurotonic states his fourth class consists of cases of traumatic nervous origin *Here one might mention that*

Muller (1891) described an attack of acute pulmonary oedema associated with angioneurotic oedema of the face

It is certain that the origin of attacks of acute pulmonary oedema varies considerably in different cases and that in most cases multiple factors are at work but it must be admitted that in some cases an attack may arise in the absence of any true weakness of the right side of the heart (as judged from ordinary and X ray and electro cardiographic examination) and without any sudden congestion of the pulmonary blood vessels due only to reflex or other disturbance of nervous centres Hess (1931 1932 1933 1939) lays stress on the probable intervention of nervous reflexes Impulses he thinks which arise sometimes but not always in the heart irritate the vasodilators of the lungs and produce active congestion together with increased transudation into the pulmonary alveoli In this process according to his views the vagus nerve plays an important part Wassermann s observation (1933) is interesting namely that in some cases pressure on the vagus fibres in the carotid (carotid sinus) can suppress the development of an attack—as it may likewise suppress some attacks of acute paroxysmal tachycardia Certain observations in experimental pharmacology speak in favour of a vagal causative mechanism in acute pulmonary oedema vagus irritation from cholines and acetylcholine (Dale 1914) vagotropic effect of pilocarpin with provocation of an attack of pulmonary oedema the effect of Sympatol during an attack in diminishing vagotonus through excitation of sympathetic fibres

We suggest that in our case the attack of acute pulmonary oedema was of pure central nervous origin due to cerebral oedema and irritation of the vagal nervous system The clinical symptoms and the rapid response to hyoscine and atropine support this view

Summary

A case is described of acute pulmonary oedema combined with hypoglycaemic coma as analogous to the cases connected with epilepsy and other cerebral disturbances Various nervous origins of attacks of acute pulmonary oedema are shortly considered

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Addendum

Dr H Pullar Strecker (*J ment Sci* 1938 84 146) knew of only four cases of acute pulmonary oedema occurring as a (most dangerous) complication in connexion with the insulin shock therapy for schizophrenia etc and referred to the following papers M Muller *Schweiz med Wschr* 1936 66 929 W Beiglbock and Th Dussik *Schweiz Arch Neurol Psychiat* 1937 39 (Erganzungsheft) 38 N Beno *ibid* 149 A Kronfeld and E Sternberg *ibid* 187 Dr Pullar Strecker kindly also gave us later references to the subject L A Finiefs *J ment Sci* 1938 84 678 S W Gillman and D N Parfitt *ibid* 718 W R Thomas and I G H Wilson H M Stationery Office 1938 22

XV

PAROXYSMAL SENSORY ATTACKS[1]

F PARKES WEBER

TRANSIENT attacks of angina pectoris are generally supposed to represent local ischaemic episodes in cases of coronary sclerosis just as the cramp like pains of intermittent claudication represent acute local muscular ischaemia connected with arterial stenosis in the extremities Certain conditions of recurrent abdominal pain have been thought (with some post mortem evidence) to be due to temporary (possibly angiospastic) ischaemic exacerbations in abdominal arteriosclerosis and by supposed analogy have been termed abdominal angina Is there real evidence that paroxysmal sensory or partly sensory attacks connected with cerebral arteriosclerosis can be explained in the same way? Following is an example of the type of case to which I refer

At the commencement of the second world war an elderly some what florid English lady married to a German long resident in England was startled by the intrusion of a policeman who simply made some inquiries into her ordinary hum drum everyday existence of which entertaining her friends to afternoon tea etc doubtless constituted a main pleasurable feature This disagreeable shock horrified her She commenced to have transient recurrent convulsive attacks (like *petit mal*) heralded by sensory aura like symptoms which latter would sometimes occur without any convulsion She was unable to describe what she felt but told me that her sensations in connexion with these attacks were so terrible that she would not wish my worst enemy to suffer in the same way The neurologist s diagnosis was that these attacks were connected with cerebral arteriosclerosis No treatment produced permanent benefit and she died ultimately in a nursing home (No necropsy)

I would ask can similar senile transient minor epileptiform attacks including sensory aurae be explained as due to cerebral arteriosclerosis in the manner suggested above?

One can also imagine that similar symptoms may occasionally occur in younger individuals and be due to arterial spasm without any underlying real cerebral arteriosclerosis just as some attacks of so-called pseudo-angina pectoris may perhaps be due to coronary spasm without coronary sclerosis In this connexion certain rare

[1]Enlarged from a letter to the *Lancet* 1949 1 39

paroxysmal sensory and psychical attacks are interesting as they may represent or be equivalent to epileptic aurae J W Fischer (*Amer Journ Med Sci* 1948 **216**, 78) describes paroxysmal attacks of cardiac pain possibly of epileptic nature The whole subject of what Sir William Gowers formerly termed vaso vagal attacks and attacks of *angor animi may be studied in this connexion* as well as the possible participation of viscero motor and viscero sensory attacks in epileptic discharges

XVI

DEATH WHILE BATHING[1]

F PARKES WEBER

THERE has often been uncertainty about the real cause of deaths whilst bathing Those who have recovered from an attack which apparently would have caused their death had it occurred while swimming in deep water can help to throw light on the subject as Alexander (1948) has done Zum Busch s account (1933) of his own experiences suggests that a kind of giant urticaria and faintness following sudden immersion in cold water may both be explained in the same way that is to say the giant urticaria as being due to the release of a histamine like substance in the skin and subcutaneous tissue which if too much gets into the general circulation may cause fainting (Horton and Brown 1929) A popular summing up of *the histamine part of the subject is given by Langdon Brown (1932)*

Every known protein contains histidine Break off a single CO molecule from this histidine and it becomes a powerful toxic sub stance histamine This substance when liberated from the tissue cells can produce all the phenomena of allergy The chemical basis of allergy is therefore simple but the factors which lead to the liberation of this substance are almost as varied as life itself Histamine was originally isolated by Barger and Dale from ergot in 1910 and then from the intestines If it is applied to the human skin it promptly raises an urticarial wheal if injected intravenously into animals it produces a condition like anaphylactic shock The problem is how does a substance which is toxic to everybody become liberated only in the tissues of certain people in answer to stimuli which are quite harmless to everyone else

Zum Busch would probably have died had he been in deep water *at the time of a severe attack There is a good deal of scattered* literature on similar severe reactions following sudden immersion in cold water But Goebel (1934) relates his personal experience when he was nearly drowned while swimming in water which was not cold on a warm summer day The accident occurred however soon after the midday meal and may have been connected with his stomach being full

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[1]Letter to the *Lancet* 1948 2 396

XVII

OPHTHALMOSCOPIC SIGN OF DEATH[1]

F PARKES WEBER

THE ophthalmoscopic sign of death – segmentation or fragmentation of the blood column in the retinal vessels – as described by Dr E A Harris (January 31 p 226) may occur at the very instant of death when the heart stops beating

Fifty six years ago (1892) when house physician at St Bartholomew s Hospital I had the following somewhat startling experience During the night another house physician asked me to see with him a patient who was comatose I wished to examine the fundus oculi with an ophthalmoscope which I had with me it was quite easy to see the disc and retinal vessels Suddenly while I was examining segmentation of blood columns occurred the patient was dead After that when called by nurses to confirm the death of patients I had opportunities to make ophthalmoscopic examinations and still have my notes on what I observed

The broken blood columns were superficially not unlike the segmented mercurial column which sometimes occurs in a thermometer or in a (too thin) manometer tube In 1892 I also noticed that the blood column segments could be moved forwards and backwards in the retinal vessels by intermittent pressure on the chest somewhat like that in artificial respiration this has apparently not been noticed by others The segmentation of the blood columns did not always occur at least not at once after death for in certain cases I failed to find any segmentation while the cornea was still not sufficiently clouded to prevent the fundus being seen In one case I noted that there was already distinct segmentation the heart having ceased to contract though the patient unexpectedly breathed once again while I was looking

The sign by itself cannot of course be actually pathognomonic of death In true embolism of the central artery of the retina segmentation of retinal blood vessels may doubtless occur at the moment of the arterial occlusion just as it may occur immediately when the heart ceases to contract at death though it is unlikely that anyone has been making an ophthalmoscopic examination precisely when the central retinal artery became occluded One may here ask when segmentation of the retinal blood columns occurs (together with

[1]Letters reprinted from *British Medical Journal* 1948 1 315 36?

cessation of the heart s action) what would happen to the eyes if *in an exceptional case* the heart w is successfully induced to contract normally again

Since 1892 I have made no further observations myself but a good deal of literature has been published notably by M H Kahn (1913 1924) After Dr Kahn s work I published some short notes of my 1892 observations (1925)

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Addendum

In my letter on this subject (*Brit Med Journ* **1**, 515) I should have worded one observation as follows In one case at least my ophthalmic examination was made some time after death but whilst the cornea was still not sufficiently clouded to prevent the fundus being seen I found *no segmentation present* Apparently there fore the segmentation sign of death had never occurred or had passed off again

XVII

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[1]Letters reprinted from *British Medical Journal* 1948 1 315 367

Raynaud's phenomena in children Certain infections play a part in the aetiology It has long been recognized for instance that congenital syphilitic children may be subject to Raynaud like attacks and attacks of paroxysmal haemoglobinuria *a frigore* There is certainly a connexion of some kind between sclerodactylia and Raynaud like phenomena Rheumatoid arthritis may possibly also be connected The puerperal condition (with or without an infection) plays an obvious causative part in the rare cases of symmetrical renal cortical necrosis in puerperal women

Results

The obvious result of local haemangiospastic attacks most to be feared is local thrombosis and permanent vascular occlusion This may lead to more or less symmetrical dry gangrene in the tips of the fingers or/and toes Permanent occlusion of a branch of a retinal artery may follow angiospasm in high blood pressure subjects A fatal result is of course to be expected in necrosis of the cortex of both kidneys once fully developed It is possible that reactive vascular dilatation following haemangiospasm may exceptionally be accompanied by haemorrhage and may thus account for certain cases of intra-ocular or cerebral haemorrhage otherwise difficult to explain

I remember an unexpected result in an infant girl aged 12 months under my hospital care in September and November 1922 [2] with recurrent attacks of Raynaud's syndrome of the extremities mostly lasting five or six hours but sometimes obviously shortened by the local application of warmth The cyanotic stage of the attacks was painful The Wassermann reaction in the child and her mother was negative The internal use of benzyl benzoate seemed to diminish the angiospastic condition but the later complete cessation of the attacks seemed to be connected with the onset of bronchitis This bronchitis however was not severe After leaving the hospital (November 17 1922) the child remained quite free from the Raynaud's attacks though on some occasions apparently she had bronchitic symptoms In April 1923 I thought she had papular urticaria of the lower limbs In 1930 I heard from a relative of the child that she remained in good health and was growing up normally (confirmed in 1936)

I am inclined to compare the well known connexion between chronic Raynaud like phenomena in the extremities and sclerodactylia with the connexion between retinal angiospasm and pigmentary

XVIII

NOTE ON HAEMANGIOSPASM ITS CAUSES AND RESULTS[1]

F PARKES WEBER

Although *it is recognized that large arteries and veins can be affected* by angiospasm especially after trauma most of the literature on the *subject* has been connected with spasm of the minute peripheral arteries and veins The superficial manifestations of such spasm and subsequent relaxation when occurring in the hands and feet—Raynaud s phenomena—have naturally attracted general attention but the symptoms of similar angiospastic processes in deeper situations are of equal or greater importance I shall not discuss here the question of the parts of the nervous and endocrine systems specially connected with vasomotor phenomena

There can hardly be any doubt that transient cerebral strokes of *various kinds are sometimes due to local cerebral angiospasm* which in many cases is certainly associated with arteriosclerotic changes some transient attacks of aphasia and amaurosis are obviously of this nature Retinal angiospasm has been observed by ophthalmoscopic examination due to the action of drugs and occasionally in the subjects of Raynaud s phenomena and high blood pressure I will not discuss here the possible role of angiospasm in migraine and paroxysmal headache

Many visceral phenomena may be of haemangiospastic origin including the rare cases of symmetrical necrosis of the renal cortex (especially in puerperal women) [1]

Causes

In some cases there *is doubtless* an inborn or acquired *tendency to* attacks of haemangiospasm analogous to the allergic tendency to asthmatic attacks which causes certain individuals to react towards mild bronchitic infections and other exciting causes (harmless to ordinary persons) by attacks of asthmatic breathing In a pre disposed subject exposure to cold (harmless to an ordinary person) may induce an attack of Raynaud s phenomena possibly leading to dry gangrene in the finger tips In predisposed subjects emotional conditions and nervous fatigue may probably favour a Raynaud like attack as they may induce an attack of asthma A condition like livedo reticularis of the skin may I think indicate a predisposition to

[1] From *Medical Press* 1948 220 272

XIX

RENAL ANGIOSPASM AND RENAL CORTICAL ANOXIA as the Cause of Acute Puerperal Anuria Calculous Reflex Suppression of Urine Traumatic Suppression of Urine (Crush Syndrome) Some Acute Toxic and Septicaemic Anurias and Anuria in Some Cases of Acute Nephrosis and Nephritis and After Loss of Haemoglobin[1]

F PARKES WEBER

THE great work in experimental pathology culminating in the publication of Studies of the Renal Circulation by Trueta Barclay Franklin Daniel and Prichard (1947) has opened up a vast number of pathogenic questions which only many years of research can answer

In 1898 Rose Bradford and Lawrence published a paper entitled Endarteritis of the Renal Arteries Causing Necrosis of the Entire Cortex of Both Kidneys The patient was an anaemic looking woman aged 36 years stated to have been quite well up to the day on which she gave birth to a dead child There was practically complete anuria from the time of her confinement until her death seven days later A few teaspoonfuls of urine which were obtained by catheterization contained a small quantity of albumin and some pus There was no fever The clinical picture was not that generally supposed to be associated with so called non-obstructive suppression of urine for though the patient gradually lost strength there was throughout a remarkable absence of the usual uraemic symptoms such as coma delirium convulsions vomiting dyspnoea and amaurosis At the necropsy practically no disease was found except in the kidneys both of which were slightly enlarged and macroscopically as well as microscopically similar to each other in appearance The necrosis of the entire cortex of both kidneys was apparently regarded by Bradford and Lawrence as due to thrombosis of the interlobular arteries – a sudden lesion perhaps in some way associated with the pregnancy It should be mentioned that though there was no fibrosis in either kidney a zone of cortical tissue just beneath the capsule and a zone adjacent to the medulla showed congestion and small cell infiltration

Several years later Griffith and Herringham (1906) described a similar case under the heading A Case of Necrosis of the Entire

[1]From the *Medical Press* 1947 218 577 and 608

changes classed under the term retinitis pigmentosa I Biro of Budapest in an article on The Present State of the Problem of Retinitis Pigmentosa [3] quotes the following observation by Redslob (1947) A girl aged 14 months a few days after fever following vaccination lost her eyesight Her retinal vessels were spastic and her fundus anaemic After some weeks the vision gradually returned but the vessels remained narrow and the discs pale Two years later an examination of the fundus showed typical retinitis pigmentosa Biro quotes analogous observations and narrates the case of a woman aged 60 years who in summer 1946 complained of recent rapid loss of sight in the right eye The fundus of the affected eye showed a marked degree of vascular spasm both arterial and venous The disc and fundus were pale No pigmentary changes were visible There was no history of any acute illness General medical and family history were negative and so was the Wassermann reaction When the patient was seen again after two years her right fundus showed retinitis pigmentosa the left fundus being still normal Biro believes that the disease in this case is due to some circulatory disturbances of unknown origin

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[1] Cf Weber F Parkes (1947) *Med Press* 218 5/2 and 608
[2] Weber F Parkes (19?3) *Brit Jnl Child Dis* 20 25
[3] Biro I (1948) *Brit Jnl Ophthalm* 32 411

further knowledge may indicate that the vascular changes found at post mortem examinations are terminal phenomena and not the primary cause of the symptoms that come on some ten days before death If the cause be toxaemia increased diuresis however obtained will aid in eliminating the toxin Crook (1927) recorded a case of puerperal renal cortical necrosis with recovery after decapsulation of the right kidney He completed H D Rolleston s review of the literature (1913)

Certain cases of suppression of urine in males help perhaps to throw light on the subject

I recorded (Weber 1909) the case of a man aged 69 years with prostatic carcinoma who died about eight and a half days after the onset of complete anuria The necropsy showed that the prostatic tumour had not obstructed the ureters for there was no dilatation of ureter or renal pelvis on either side There was evidence of old chronic interstitial nephritis in both kidneys but the epithelium of the renal convoluted tubules had more or less all of it undergone a necrotic change the secreting cells had a granular woolly appearance and hardly took on the logwood stain at all their nuclei had mostly disappeared (karyolysis) or could hardly be distinguished from the cytoplasm The other renal tubules glomeruli and blood vessels showed practically no changes excepting those due to a certain amount of old chronic interstitial nephritis None of the blood vessels seemed to be thrombosed The thrombosis of the interlobular arteries described in earlier cases can I think hardly be regarded as the primary cause of the cortical necrosis in any of the cases but it was rather in some way secondary to the changes in the secreting tubes My case illustrated the association of fatal so-called non obstructive anuria with widespread necrosis of the secreting cells of the renal convoluted tubules without signs of thrombosis of renal blood vessels It seems to me that the change in the renal convoluted tubules may be merely an extreme degree of the change known (in its earliest form) as cloudy swelling and that it indicates a condition of acute nephrosis supervening in previously chronically diseased kidneys

Preston King (1909) recorded the case of a rheumatic man aged 58 years who had a sudden attack of epigastric pain followed by vomiting and absolute suppression of urine until his death seven days later There was no uraemic smell in his breath or skin and his mind remained perfectly clear to within five hours of his death The necropsy showed the right kidney represented by a small thin walled

Renal Cortex of Both Kidneys together with Thrombosis of All the Cortical Arteries occurring in the Puerperal State. The patient was a multipara aged 35 who however had had symptoms of chronic *nephritis for* several years. At the necropsy renal cortical necrosis, thrombosis of the interlobular arteries and areas of small cell infiltration were found as in Bradford and Lawrence's case but there were *decided changes due* to chronic interstitial nephritis and practically no evidence of endarteritis.

Lloyd of Melbourne Australia recorded (1906) an almost identical case. *A multipara aged 39 years was delivered* of a stillborn child and from that time she passed no more than eleven ounces of urine (containing albumin) till her death eleven days later. There were several *eclamptic convulsions during the first few hours after* delivery and later some vomiting and uraemic twitchings but consciousness was preserved till the end. There was no fever. At the necropsy the kidneys closely *resembled those in Bradford* and Lawrence's case but microscopically as in Griffith and Herringham's case there was evidence of chronic interstitial nephritis without obvious endarteritis.

After the foregoing publications various cases of puerperal bilateral renal cortical necrosis were published. Jardine and Teacher (1909) suggested extreme tonic contraction of the small renal blood vessels as a causal factor in determining the onset of thrombosis.

In the case of a woman aged 29 years Torrens (1911) reported that at the necropsy the ovarian and renal veins were found thrombosed throughout (the right renal and ovarian veins opened simultaneously into the inferior vena cava) the clot did not appear septic. There was no atheroma or endarteritis of the renal arteries. The kidneys weighed eight ounces each. The capsules strip readily exposing a smooth mottled red and yellow surface. On section the entire cortex is pale buff in colour and is surrounded by a bright red line of hyperaemic reaction: the pyramids are dusky red *and stand out* distinctly in contrast to the pallid cortex. Microscopically the kidneys show general infarction of the cortex. There is haemorrhage into the *tubules and glomeruli but no evidence of endarteritis*: the venules however appear thrombosed. This was apparently the first of such cases in which thrombosis of the renal veins (extra renal) was *reported*: according to Adami and Nicholls (1910) obstruction of veins can produce a condition of infarction.

Clifford White (1918 and 1919) reported two cases of Puerperal Anuria in which recovery followed nephrotomy. He suggested that

literature of the subject analysed 64 cases and stated that the condition may apart from pregnancy occur in a variety of infectious diseases it may follow trauma and develop cryptogenically In regard to treatment he admits that decapsulation of the kidneys or nephrotomy may favourably influence an otherwise refractory angioneurotic anuria

Madding Binger and Hunt (1940) mention a case resembling puerperal bilateral renal cortical necrosis in which quinine given by the mouth for the induction of labour may have acted as an aetiological factor

De Navasquez has thrown much light on the present subject by his work on Experimental Symmetrical Cortical Necrosis of the Kidneys produced by Staphylococcus Toxin (1938) also on a related subject by his work (1940) on The Excretion of Haemoglobin with special reference to the Transfusion kidney

Doniach and Walker s paper (1946) on Combined Anterior Pituitary Necrosis and Bilateral Cortical Necrosis of the Kidneys following Concealed Accidental Haemorrhage is an important one and is duly stressed in Studies of the Renal Circulation by Trueta Barclay Franklin Daniel and Prichard (1947) From this last already mentioned work I will quote (p 138)

> Our experimental findings lend support to the theory that *renal anoxia* or as we should term it *cortical anoxia* plays an important part in the development of the renal failure in cases of *crush syndrome* As we envisage it the diversion of the blood flow from the cortex is not so complete as to result in a total ischaemia since we are not aware that any case of complete cortical necrosis has been reported in crush syndrome The pallid cortex with its ischaemic glomeruli favour this explanation of the cause of the anuria Darmady (1947) reports 17 cases of which 5 recovered of a syndrome of traumatic anuria (p 139) Changes in both the function and the morphology of the kidney somewhat similar to those observed in both crush syndrome and traumatic uraemia may be seen in a number of other conditions for instance in cases of incompatible blood transfusion excessive vomiting septic abortion concealed accidental haemorrhage Weil s disease sulphonamide kidney blackwater fever and cholera

One of these authors fundamental conclusions is that the autonomic nervous system plays a direct part in controlling renal function It seems to me that quite a minor illustration of this conclusion is afforded by the diuretic or polyuric crises which have

irregular cyst containing some clear fluid and its ureter was a solid cord The *left kidney was enlarged weighing seven ounces and there* were many small cysts on its surface containing a turbid yellow fluid On section it was engorged the capsule stripped readily and the pelvis was injected There was no calculus or other form of obstruction either in the kidney or ureter which was patent throughout Microscopically the epithelial cells of the convoluted tubules were small and misshapen their protoplasm granular and their nuclei indistinct many tubules contained coagulated material the glomeruli showed no noteworthy changes There was much small-celled infiltration around the blood vessels and an increase of connective tissue in the medulla *Preston King points out that if a calculus had been found* the case would have been one of calculous anuria with nothing specially remarkable about it

I would include as examples of the same class of anuria all cases of calculous suppression of urine not due to complete obstruction and apparently of a reflex nature

Wordley (1923) described a case of Cortical Necrosis of the Kidney with *Polyarteritis Acuta Nodosa* The patient was a boy aged 15 years He had had very severe spasmodic pains in the right side of the abdomen with fever this was followed in a week s time by haematuria and suppression of urine both of which were only temporary He died about six weeks after the onset of the haematuria The necropsy showed typical polyarteritis nodosa of the heart the kidney change seems to me to have been one more of polyarteritis nodosa than of typical cortical necrosis

Bamforth (1923) described A Case of Symmetrical Cortical Necrosis of the Kidneys occurring in an Adult Man The patient *aged 37 years when suffering from an uncertain febrile illness* ceased to pass urine two days before his death On account of a suspicion of malaria 20 grains of quinine hydrochloride were given intravenously at about the time when anuria was noticed At the necropsy there was no evidence of increase in the interstitial tissue of the kidneys There was no endarteritis of renal arteries and no thrombosis of the renal veins

Ash (1933) wrote a paper on Bilateral Cortical Necrosis of the Kidneys making his idea of the pathogeny of such cases clear by adding to his title the words Angioneurotic Anuria This term he adopted to include all non obstructive anurias regarding bilateral renal cortical necrosis as a pathological term applicable only to the terminal stage of certain cases He gave very many references to the

was employed for general anaesthesia In some cases anuria was a striking symptom and sometimes changes have been found in the kidneys corresponding to those in the liver In certain cases there has been reason for believing that the liver was already diseased or imperfectly functioning before the operation Many other drugs (including trilene) have occasionally acted on the liver in the same way Compare F Parkes Weber *International Clinics,* 1920 Series 30 4, 54 and *Clinical Journal* London 1921 **50** 165

In regard to renal anoxia B G Maegraith and others (*Lancet,* 1945 **2,** 293) referred to similar renal changes in numerous conditions and they speak of an analogou *hepato renal syndrome* as well as a *renal syndrome* T F Hewer and R F Woolmer (*Lancet* 1947 **2** 909) describe what they regard as renal anoxia after myanesin anaesthesia —a post operative death from uraemia in a woman aged 22 years the necropsy findings in the kidneys being similar to those occurring after severe haemoglobinuria from incompatible blood transfusion

often been observed when supposed hysterical or functional nervous attacks of various kinds are subsiding (? dilatation of blood vessels following angiospasm)

Lastly the consideration of angiospasm in renal arteries brings up the whole question of arterial angiospasm in other parts of the body The typical acute phenomena observed in the extremities in cases of Raynaud s disease cannot be explained except in connexion with angiospasm and indeed temporary angiospasm of a branch of the retinal artery of one eye has actually been seen in certain patients by ophthalmoscopic examination in connexion with Raynaud s disease Transient recurrent cerebral fits hemiplegia aphasia amaurosis etc have with great probability been attributed to angiospasm in individuals with arteriosclerosis or high blood pressure Clinically evidence of angiospasm of larger arteries for instance temporary disappearance of the radial pulse on one side has been rarely but definitely observed in the same class of patients

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Addendum

In regard to this whole subject one is reminded of the cases of so-called late chloroform poisoning in which death from acute or subacute hepatic necrosis followed operations in which chloroform

He called it anaphylactoid purpura and rapid return to normal followed spontaneous abortion It was not a case of so-called purpura haemorrhagica but amongst the 47 published cases of purpura complicating pregnancy collected by Rushmore there were some in which the mucous membranes were severely involved (purpura haemorrhagica) In some of the cases the purpura appeared with each pregnancy but never apart from pregnancy Apparently the thrombocyte count when taken was generally not abnormal [1]

When a *menstrual eruption* is *haemorrhagic* it has usually been explained as an example of supplementary menstruation as it has been supposed to reinforce the true menstrual loss—or else vicarious menstruation if it seems to occur instead of and completely replace normal menstruation It is to the consideration of haemorrhagic menstrual eruptions that we shall here confine our attention

F Hammer [7] in his account of Idiopathic or Essential Forms of Purpura (1928) includes a reference to *haemorrhagic menstrual exanthemata* and notably to Paul Opel s work on the subject (1908) [8] Purpura with ecchymoses may indeed occur in connexion with menstruation as may various other eruptions especially erythemata and urticaria Such cutaneous haemorrhages are often preceded by urticarial erythema and improve when menstruation commences Roger and Collard [9] described a case in which purpuric patches appeared over the whole body at the beginning of the first menstruation The menstrual purpura recurred every month for many menstrual periods but finally completely disappeared after pregnancy In other cases however pregnancy did not prevent the menstrual eruption from reappearing later on

J Weitgasser and K Cafasso [10] described a case of menstrual urticaria haemorrhagica in a woman aged 23 which apparently by the old terminology would have been classed as an example of supplementary menstruation

A Hauptmann in 1909 [11] described a remarkable case of

[1]Evidence of the profound influence of pregnancy and the menstrual state in some women on the vascular system is furnished by rare cases in which telangiectatic or haemangiomatous patches appear in connexion with pregnancy In some cases such patches may recur with subsequent pregnancie At the Clinical Section of the Royal Society of Medicine (*Proc* 1949 42 516) W A Bourne and J K Wagstaff showed a woman aged 32 years with a telangiectatic patch on the right shin and persistent telangiectatic redness of the thenar and hypothenar eminences The redness of these areas increased at the menstrual periods during which the patient had variable epistaxis The leg patch appeared during the patient second pregnancy

XX

RECURRENT MENSTRUAL PURPURA AND VICARIOUS MENSTRUATION[1]

PHILIP ELLMAN and F PARKES WEBER

In this paper it is not our purpose to discuss all forms of menstrual eruptions the commonest of which is probably premenstrual herpes of the lips and nose They obviously are all at least partially dependent on an endocrine or metabolic change of some kind associated with and causally connected with the menstrual periods just as some of the rare eruptions complicating pregnancy are obviously partially due to analogous changes connected with the pregnant state of the mother and possibly with the metabolism of the foetus In regard to both menstrual and puerperal dermatoses from the pathogenetic point of view one would have to consider metabolic changes connected with the functions of menstruation and pregnancy temporary functional changes in the endocrine organs the possibility of diminished resistance towards infections and autogenous toxins and (especially in regard to dermatoses of pregnancy) the question of allergy or anaphylaxis

In regard to the influence of metabolic changes it should be noted that the dermatoses of pregnancy have been regarded as toxicodermias due to intoxication by a product of albuminous catabolism in the maternal organism (L Seitz quoted by A Lysander [1]) H Mommsen [2] has no doubt as to the existence of a menstrual toxin though its exact nature is uncertain It is probably he thinks a substance or a mixture of substances derived from lipoid metabolism In regard to the endocrine organs one may remember the recorded cases referred to by Paul Opel [3] in which hypertrichosis (face etc) accompanied pregnancy in Slocum s case a growth of facial hair accompanied each pregnancy [4] As to the possibility of temporary diminished resistance to infections we would call to mind Virchow s case [5] of a girl who (once) during a menstrual period acquired facial erysipelas This afterwards recurred frequently with menstrual periods In respect to the possible influence of allergy or anaphylaxis Stephen Rushmore s paper on Purpura Complicating Pregnancy [6] may be consulted Rushmore s only personal case was one in which purpura occurred at the sixth month of the first pregnancy It was associated with much pruritus but no urticaria

[1]After the *British Journal of Dermatology and Syphilis* (1935) 47 193



FIG 1

fingers going dead but not much during the last years She says she had scarlet fever at 12 years slight anaemia at 17 years and gastric ulcer at 50 years of age She had had five children no miscarriages Three of her children are living and healthy one of her children died at the age of 12 years during the influenza epidemic of 1918 the remaining one died at 2 years of epidemic cerebrospinal meningitis in 1916

Treatment by calcium gluconate (intramuscular injections of 5 c c of a 10 per cent solution) and glandubolin (Richter) (intramuscular injections of 1 c c) has undoubtedly done good

Results of various examinations – Brachial blood pressure monthly readings have averaged 155/90 mm Hg Wassermann and Kahn reactions with the blood serum negative Bleeding time (Wright s technique) 160 seconds (normal 150–180) Blood-coagulation time after Landau 2 minutes 25 seconds (normal average 1 minute 45 seconds) Blood count Haemoglobin 100 per cent erythrocytes

haemorrhage into the upper and lower lips of a girl aged 18 as an example of *vicarious menstruation*

Our present case is that of an otherwise apparently normal woman (Mrs M C) aged 58 who ever since the age of 47 has been subject to recurrent *purpura limited to her lower extremities* Her menopause was between 52 and 53 years of age Until the menstruation ceased her purpuric attacks might have been regarded as supplementary menstruation Afterwards they might be called 'vicarious menstruation Before the menopause the purpura appeared in small spots only but after the menopause the attacks became worse recurring at first every month but later on every two months Together with the purpuric spots (macules) there were then large ecchymotic patches on the portions of the extremities below the knees and sometimes swelling of these parts accompanied the attacks The purpura has been accompanied by a good deal of pain and sometimes there has been a slight feeling of sore throat at the commencement of the attack The attacks have usually lasted about a week before the purpura begins to fade The fading takes place suddenly and in about two weeks as a rule all trace of the purpura have disappeared Mental shock can apparently make the attacks worse

One of us (Ph E) first saw the patient in August 1933 when the attacks were very bad recurring about every other month and accompanied often by swelling of the feet and legs The appearance of the ecchymotic patches and purpuric spots during a typical attack in 1934 is well shown in the photograph (fig 1) It is clear that the eruption is not quite symmetrical The irregular outline of the ecchymotic patches when commencing to fade in their central portions reminds one somewhat of large patches of polymorphic erythema (erythema multiforme) Some of the spots are very slightly raised In one of the recent attacks there were a few purpuric spots above the previously highest upper limit the purpura in front reached about three fingerbreadths above the inguinal fold during the attack in question

The type of purpura most resembles the mixture of erythema and purpura (purpuric erythema) known as the Schonlein Henoch or anaphylactoid type for which an allergic or anaphylactic causation is probable as it is certain for urticaria Examination of the patient s blood has shown nothing special excepting a slight diminution of thrombocytes

In regard to the past medical history it may be noted that the patient since the age of 45 years has often suffered from some of her

XXI

WEBER CHRISTIAN DISEASE OR RELAPSING FEBRILE NODULAR NON SUPPURATIVE PANNICULITIS[1]

ALICE CARLETON

THOUGH early cases of this condition were described by Pfeifer in 1892 and by Gilchrist and Ketron in 1916 the first authoritative account was given by Parkes Weber in 1925 under the name of Relapsing Nodular Non Suppurative Panniculitis In 1928 Christian observing that a rise of temperature was a characteristic feature not seen in other forms of panniculitis added the term febrile to the title Since then 48 cases have been described (Pfeifer Gilchrist and Ketron Parkes Weber (2) Christian Alderson and Way Netherton Brill Bailey (5) Reed and Anderson Puente Cummins and Lever (2) Shaffer Binkley Sweitzer Machacek Mengoli Tilden Gotshalk and Avakian (2) Ziegert Skiold Hartwell and Thannhauser Hanson and Fowler Larson and Ootkin Carol (2) Pinetti Fraser Rosenberg and Cohen Lowry Miller and Kritzler Arnold Spain and Foley Larkin de Sanctis and Margoulis Pierini Irigoyen and Ugazio (4) Ungar Mostofi and Engleman Baumgartner and Riva Zee Bunnell and Levy) It is difficult to decide whether some cases published as Relapsing Nodular Non suppurative Panniculitis should be included in this list or not as the criteria are somewhat indefinite Hazel s case has been omitted as more properly belonging to another category Pinetti excludes the cases of Pfeifer Netherton Machacek and the first case of Cummins and Lever largely because they were non febrile Those interested in the condition are referred especially to the papers by Larkin *et al* Pinetti and Baumgartner and Riva

The disease may be heralded by vague malaise with aching joints and muscles or it may begin directly with the appearance of nodules in the subcutaneous fat At first deep-seated and palpable only they later become visible as firm rounded elevations In the early stages the epidermis is not involved but by degrees it develops an orange skin texture and a variety of inflammatory discolorations Though nodules may evolve without subjective symptoms and even without the knowledge of the patient they are more often tender and some times painful It is rare for the surface to break down The usual course is a leisurely regression and as the fat is absorbed the skin

[1]From the Department of Dermatology Radcliffe Infirmary Oxford

4 800 000 leucocytes 5 600 (eosinophils 2 4 per cent basophils 0 4 per cent polymorphonuclear neutrophils 74 8 per cent lymphocytes 19 6 per cent monocytes 2 6 per cent) slight anisocytosis thrombocytes 154 000 per c mm of blood Blood calcium 9 mg per cent Blood phosphorus 2 5 mg per cent The last two estimations were made by Dr David H Haler on October 18 1933 the other data (excepting the blood pressure readings) are of October 5 1933 Charts of temperature pulse and respiration in January and February 1934 when there was slight purpuric recurrence showed nothing abnormal excepting that the pulse was sometimes between 80 and 90 per minute

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Fig 1 —Distribution of lesions




Fig 2 —Note deep hollows beneath both malar bones on the left temple and beneath the jaw on the left side

becomes sucked in to the underlying fascia creating a very characteristic deep saucer like depression Fever usually accompanies the eruption of a group of nodules and after an intermission the whole process is repeated The histology is characteristic being a necrosis of fatty tissue with a secondary cellular reaction but it has a superficial resemblance to the reaction elicited in the subcutaneous fat by camphor injections and other forms of trauma

Case Report (R I Regist No 83512/48)

Mrs C W a German Jewess born 1912 Early in 1942 she felt a general aching as though she had slept on a hard bed This continued and she began to lose weight and to have night sweats In March 1942 following a localized pain in her left forearm a hard pea sized nodule became palpable It was tender to the touch Nodules from pea to walnut size then appeared with a markedly symmetrical disposition On the arm they outlined the deltoid and triceps one was found on the front of both forearms and in the middle of the buttocks A string of nodules marked the iliac crests The only asymmetrical ones were on the right thigh and on the left of the umbilicus Some were heralded by pain but others were at no time painful or tender The nodules grew slowly in size and four months later they had developed into elevations from ½ to 1½ inches in diameter The skin over them was fixed and reddish blue but in the nodules of the gluteal region atrophy was already manifest The patient was admitted to a London hospital in August when further nodules were found of whose existence she had not been aware in the middle of the back at the inferior angles of both scapulae and in the left breast The breasts were scarred as a result of a plastic operation performed in Berlin in 1927 for aesthetic reasons While in hospital she ran an evening temperature of 99° F to 100° F for a couple of weeks One of the nodules was removed and it was reported that it showed dense fibrosis of the dermis with mucinoid degeneration while the muscle showed foci of chronic inflammation and a diagnosis of dermatomyositis was made (The section was later re-examined and had the features of a non suppurative panniculitis) Her B M R was normal Creatinine excretion was 520 mg in twenty four hours An E S R was 57 mm /hr (Westergren) She was treated with thyroid gr ½ t d s She left hospital in September Shortly after fresh nodules appeared beneath each malar bone on the left temple and beneath the jaw on the left side Her temperature was not taken on this occasion In February 1943 she wrote that her

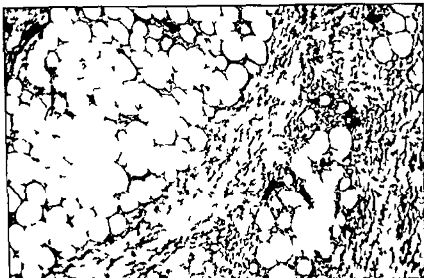


FIG 5—Acute lesions showing interstitial oedema and necrosis of connective tissue stroma of adipose tissue The interstitial reaction is still limited to the collagenous septa where there is fibrin and fibrinoid exudation (From Dr Robb Smith)

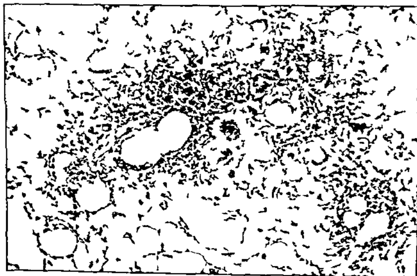


FIG 6—Chronic lesion showing areas of scarring lymphocytic infiltration and macrophage ingestation of broken down fat cells (From Dr Robb-Smith)

Fig 3.—Deltoid and triceps outlined by hollows

Fig 4.—Atrophic hollows at margins of deltoid and on left forearm

especially the thighs and lower trunk The nodules are generally asymmetrically distributed

Regression occasionally the nodules break down and ulcerate and a little oily yellow brown fluid exudes Some of the smaller lesions may leave no trace But characteristically the hard nodule softens to the consistency of a lipoma there is some transient pigmentation and a saucer like depression lined by normal epidermis is left The hair is rarely involved but when it is as in Pinetti s case there is a temporary alopecia

Interval between eruptions from a few days to several years It is therefore rash to claim a cure unless a free interval of many years has resulted

Pain and tenderness common but not invariable

Temperature usually 99° to 100° but 105° has been recorded The fever may precede accompany or follow the eruption of the nodules It may last a few days to several weeks Not all cases nor all eruptions in an individual case are accompanied by fever

Sex Of 49 cases 35 were women

Age from 6 months to 70 years The average age is 35

Histology —Though most observers describe this as non characteristic a different opinion is held by Dr Robb Smith who has kindly supplied the following account —

The histology is characteristic There is a necrosis of connective tissue septa around the fat cells over a considerable area without vascular or cellular reaction At the periphery of the necrotic lesion a cellular and oedematous reaction occurs at first neutrophil leucocytic which is not marked then a histiocytic reaction with plasma cells and lymphocytes and subsequently a fibrosis with the formation of lymphoid aggregates In a necrotic zone there is at first no change in the sudanophil material in the fat cells Then fragmentation and dissolution of the sudanophil material occurs with the appearance of fatty acid crystals fat-containing histiocytes and various types of inclusion bodies such as are seen in all forms of fat necrosis

The feature of the morphological lesions which distinguishes them from those seen in traumatic fat necrosis is that in the early stage there is no vascular damage or haemorrhage in an infective fat necrosis such as occurs at the edge of a purulent cellulitis there is always an inflammatory cellular reaction of the interstitial tissue before necrosis occurs in a fat necrosis such as follows the injection of a chemical irritant the appearance may be very similar but usually there is greater cellular dissolution

aching pains had come on again but apparently no nodules followed and she had an intermission of four years during which her health was good except for a varicose eczema of both legs At the end of January 1948 the pains once more returned and a nodule appeared in the right breast As it was thought that this might be a carcinoma she was referred to the surgical department of the Radcliffe Infirmary and the nodule was excised Dr Robb-Smith reported as follows (R I S H 673/48 981/48) Extensive fat necrosis with numerous foreign body giant cells at the periphery of the lesions some containing a Wolbach stellate inclusion others containing anisotropic apparently crystalline material The necrosis of the adipose tissue is quite diffuse and at the periphery of the necrotic areas there is a cellular reaction chiefly lymphocytic and with plasma cells, though small numbers of neutrophil leucocytes are present There is some sclerotic reaction and the appearances would be consistent with a non suppurative panniculitis The breast tissue proper showed marked fibrosis of its stroma and atrophy of the gland tubules There is no evidence of neoplasia The summing up was Fat necrosis—Non suppurative panniculitis As a result of this report the patient was transferred to the Skin Clinic She was found to be an obese woman with saucer like depressions on the areas already described The remarkable symmetry exhibited by this case is quite unusual and has only been reported once before by Pfeifer On general examination the patient was found to be a healthy woman with nothing significant in her previous or in her family history Nervous system thoracic and abdominal viscera mouth nose and throat showed nothing abnormal

Blood picture normal Leucocytes 7 000 Chest and spine X ray normal W R and Kahn negative Agglutination to Brucella abortus negative Blood culture micrococci only E S R 56 mm /hr

The patient left the country before any treatment was initiated She was seen by Dr Parkes Weber who considered her a classical example of the disease

When the picture is so complete there is not much difficulty in making a diagnosis But borderline cases are by no means easy to place and indeed with further knowledge the list of cases referred to above may have to be revised and some perhaps placed in another category It may therefore be useful to give more precise details of the possible variations in the general picture

Number of nodules 1 to 20 in each crop

Site any part of the body from the scalp to the extremities but

dermatitis herpetiformis and the sensitivity in both diseases to iodides and bromides

A clearer understanding of the Weber Christian disease may be achieved by enlarging the field and considering non suppurative panniculitis in general This term (the German speaking peoples prefer the title Lipogranuloma) is applied to a non specific reaction of the subcutaneous fat Various efforts have been made to classify the different types efforts which have been handicapped by our scanty knowledge of the reactions of this tissue The following classification is put forward as a simple outline with no claim to be complete or finally correct

1 Secondary panniculitis as a direct response to a neighbouring tissue disturbance such as phlebitis or mastitis or tumour metastases

2 Traumatic panniculitis

(a) Due to mechanical injury Adiponecrosis subcutanea neonatorum has generally been considered as coming under this heading It appears in the first ten days of life without any general disturbance Resorption with only slight atrophy takes place in a few weeks or months Cases have been said to follow difficult labour or artificial respiration But in a recent paper Flory (1948) has collected four cases including one of his own in which the infants died from other causes and in each case post mortem examination revealed fat necrosis in the viscera He considers that cold and trauma can hardly cause deep seated visceral fat necrosis and points out that in any case the term subcutaneous should be dropped

Better examples of this group are the panniculitis that follows a blow on the breast or the nodules that appear in amputation stumps on the pressure areas

(b) Due to chemical injury from subcutaneous injections Examples are the well known oil granuloma following camphor injections or the paraffinoma which was sometimes a sequel to the injection of paraffin wax for aesthetic purposes As one would expect the panniculitis appears on the site of the injection but some paraffinomata arose in distant sites and one must assume a metastasis of the injected material Many substances even such innocent ones as Ringer s solution have induced a nodule of panniculitis

(c) Due to thermal injury climatic or therapeutic Both freezing with CO snow and heating with diathermy may produce panni

I have not had an opportunity of studying lesions in the Rothmann Makai type of panniculitis and the description given by *Baumgartner and Riva* is not detailed enough to allow any conclusions to be drawn as to its resemblance to the lesions in other forms of panniculitis

Clinically the salient features which distinguish Weber Christian disease from other forms of non-suppurative panniculitis are the absence of any manifest predisposing cause the rhythm of alternating activity and freedom the accompaniment of fever and general systemic disturbance and above all the characteristic form of the terminal atrophy

Thorough investigation of a number of cases has produced no clue as to the cause of the disease Both tuberculosis and syphilis can be ruled out though in a group of cases positive evidence of one or other disease will occasionally be found The blood picture varies It is often normal sometimes there is a leucocytosis sometimes a leucopenia Blood cultures are sterile tests for Brucella typhoid para typhoid and dysentery are negative Focal infection has been found in over a third of the cases *in the form of infected tonsils* dental sepsis or sore throat Such infection may of course be without causal significance But occasionally a connexion between the focus *and the eruption is clinically underlined In Miller and Kritzler s* case a dental extraction was twice followed by the eruption of nodules There was an interval of two months but in panniculitis *following trauma or typhus fever a long latent period is also found* In the case of Baumgartner and Riva it happened three times that an attack of tonsillitis was followed a month later by a crop of nodules *Alderson and Way s case was a sequel to streptococcal infection of a* finger and Mengoli s occurred in the convalescence after typhus In some cases (Weber s second case 1935 two of Bailey s Rosenberg s and Ungar s) iodides or bromides appear to have initiated or aggravated an eruption

As might be anticipated *treatment* has given almost uniformly negative results Arnold s case however is of particular interest in this respect For over a year his patient was given a daily dose of 3 5 grammes of sulfapyridine On five occasions a relapse occurred when the drug was discontinued and each time remission followed twenty four hours after its renewal Each relapse was associated with a raised F S R Arnold thinks these facts suggestive of a bacterial allergy and draws attention to the similarity of response in

5 Necrobiosis lipoidica diabeticorum The early lesion is a sharply marginated red papule This develops into a firm flat plaque with a yellowish centre which looks as if it were covered with a tightly stretched layer of cellophane

It is hardly necessary to dwell on the points which differentiate panniculitis from iodide or bromide granulomata scleroderma or circumscribed myxoedema

Etiology —One can only indicate some observations of potential interest There is an ill defined connexion between panniculitis and lipomata After the destruction of fat there may be an excessive rebound with the formation of a fatty tumour Lipomata may follow injuries to the CNS and according to Baumgartner and Riva panniculitis has been seen as a sequel to tabes polyneuritis and alcoholic neuritis

An observation of great interest was made in 1946 by F Duran Reynals A number of rabbits which were being used for experimental purposes developed mild haemorrhagic necrotic nodules in fat and muscle especially the psoas muscle These were observed to follow inoculations of different kinds such as viruses bacteria tissue extracts and even Ringer s solution After the affected animals had been killed and studied some apparently healthy contacts were killed It was found that they too were affected especially in the retroperitoneal fat along the psoas though not to a sufficient extent to make a diagnosis in life possible It needed some non specific stimulus to elicit the clinical phase Histologically the nodules showed an inflammation with fat necrosis which proceeded to fibrosis and slow absorption The disease took on an epidemic form but no agent could be found either on direct examination or on culture A virus was suspected It was found on enquiry that rabbits in other laboratories in the U S A had had a similar affliction

Six cases of Weber Christian disease have died though seemingly not as a result of the condition One of Bailey s cases and one of the two described by Tilden and his colleagues died of tuberculosis In Miller and Kritzler s case the nodules ulcerated and death occurred from exhaustion and hepatic failure Mostofi s case died of broncho pneumonia Spain and Foley s of glomerulonephritis and Ungar s of acute peritonitis In the last three cases post mortem examination showed numerous necrotic nodules in the abdominal and thoracic fat It is obviously desirable that all cases of Weber Christian disease should be investigated after death to determine how often the e deeper fat depots are involved and to what extent the disease

culitis Young children sometimes develop nodules on the fore head cheeks and chin from exposure to extreme cold

(*d*) Due to bacterial toxins Various Russian authors (Abrikosoff Garschin and Weil quoted by Baumgartner and Riva) have described a liponecrosis of the inner side of the legs which comes on in from a few weeks to eighteen months after typhus and ends with atrophy Histologically it resembles an oil granuloma

In all these forms there may be a latent *period of weeks to years* before the tissue reaction is clinically apparent It is reasonable to suppose that since the injuries are common and the result rare such a *tissue response* argues an abnormal sensitivity or reactivity *of the* fatty layer

3 Primary or Spontaneous panniculitis

(*a*) Weber Christian disease

(*b*) Panniculitis of Rothmann Makai This title is suggested by Baumgartner and Riva for a rather ill defined group of cases much more commonly seen than the true Weber Christian This type differs from the latter in the absence of intermissions or of any general disturbance or fever and the terminal disappearance with out a trace The whole rhythm of the Rothmann Makai type is different the nodules arise quickly sometimes in the course of a night and after a varying period are resorbed without atrophy According to Baumgartner and Riva a significant number of cases occur in psychopathic individuals and arthralgia and neuralgia are commonly associated Though the disease may arise in a healthy individual it is more usually a sequel to infection such as tonsillitis phlebitis or bronchiectasis It is likely that further knowledge will lead to more precise delimitation of this group

Differential diagnosis

1 Erythema nodosum This tends to be seasonal and is generally confined to the legs and arms The nodules are soft superficial and resolve rapidly leaving no mark

2 Sarcoid of Darier Roussy is persistent and does not occur in repeated bouts with associated constitutional disturbance The atrophy is not saucer like

3 *Erythema induratum of Bazin is almost confined to the legs and* tends to ulcerate leaving a slight flat atrophy

4 Adiposis dolorosa of Dercum There is a nodular form of this condition which appears *in bouts associated with fever and malaise* But the nodules are generally permanent and never leave saucer shaped depressions

XXII

IDIOPATHIC EXTREME OSTEOPOROSIS ESPECIALLY OF THE SPINAL COLUMN AND THORACIC CAGE WITH COLLAPSE OF FRONT OF CHEST[1]

H C LAUBER F PARKES WEBER and J G GREENFIELD

By idiopathic we mean of unknown causation Burrows and Graham (1945 and 1947) describe a condition of spinal osteoporosis of unknown causation due to deficient ossification affecting adults above 30 years of age mainly women of 55 to 80 but also men commonly between 40 and 70 Though the cause is unknown it is suggested that it may possibly be related to slight dietary deficiency of calcium phosphates and ascorbic acid but it is not due to deficiency of vitamin D With calcium medication they say the symptoms improve but there is little or no demonstrable improvement in regard to the osteoporosis

They write Although generalized osteoporosis can sometimes be demonstrated a *material degree of porosis* is confined to those bones which in the adult contain red bone marrow namely those of the spine limb girdles and thoracic cage Only the lumbar and thoracic vertebrae undergo sufficient porosis to suffer *material deformity'* Our present case differed from all the severe ones to which Burrows and Graham (1947) refer inasmuch as the actual bony collapse was relatively slight in the vertebral column but so extreme in the thoracic cage as to cause collapse of the front wall and falling in of the sternum

Account of the Case

The patient a manufacturer aged 44 years was admitted to Hospital under Dr H C Lauber on November 12 1943

History —The family history was not relevant There were no brothers or sisters In 1923 chronic cholecystitis with hypochlorhydria had been diagnosed (dislike of fatty food blown up feeling flatulence) Since 1930 he had suffered on and off from fibrositis In 1937 a tumour of the brain was diagnosed by Dr H Cohn and operated on by Sir Hugh Cairns An oligodendroglioma was removed After that the patient felt well except that in 1940 he suffered from sinusitis

Since January 1943 he had from time to time noticed pain in his back for which he had massage The pain gradually got more severe

[1]Reprinted from *Annals of Rheumatic Diseases* 1948 7 17

resembles the nodular fat necrosis described in animals by Duran Reynals

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For histological illustrations of the lesions in this disease the reader is referred also to the original papers of Weber (1925) and Christian (1928)

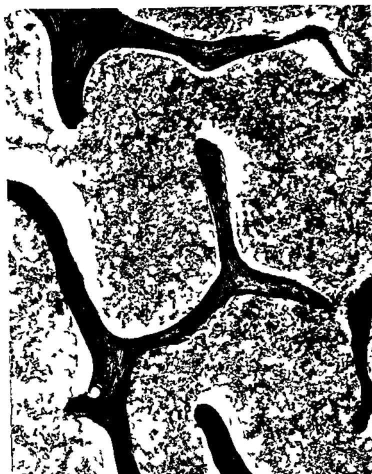


Fig 2—Section of vertebral body showing very thin bony trabeculae In this area the loss of marrow cells is only slight ×55

organs abdomen and central nervous system were normal The dorsal and lumbar spine was stiff and most painful when bending down or sideways The joints of arms and legs were normal and so was the temperature Cholecystography showed that the gall bladder did not fill The Wassermann reaction was negative The erythrocyte sedimentation rate was 28 mm (two hours average) The urine contained a trace of albumin no sugar a few hyaline casts and no Bence Jones protein

The blood count was haemoglobin 70 per cent erythrocytes



FIG 1 —Section of skull showing rather thinned trabeculae of bone in diploe and partial disappearance of marrow cells × 55

and in October he noticed that he could lie in a certain position only and that the pain was most pronounced on getting up in the morning At the beginning of November 1943 the pain was especially felt in his right side and he went to hospital with the suspicion of having pleurisy

Condition in hospital —He was a thinnish pale looking man without dyspnoea and without cyanosis Cardiovascular system chest

122 mg per 100 c c On December 15 there was a trace of albumin in the urine and also a few hyaline and granular casts The blood urea was 137 mg per 100 c c

Urological examination (Dr Dannheisser) did not show signs of obstructive uraemia Fluid intake was 55 ounces and fluid output 48 ounces

At the end of December the blood urea was 103 6 mg per 100 c c

By January 1944 the patient recovered from this uraemic condition He complained of increasing pain in the back and chest on and off His anaemia increased his strength deteriorated though his appetite was very good On January 15 the blood count was haemoglobin 40 per cent erythrocytes 1 980 000 per c mm of blood colour index 1 02 leucocytes 7 800 per c mm The differential count (per cent) was neutrophils 36 neutrophils stab 8 neutrophils juv 1 lymphocytes 51 monocytes 2 eosinophils 2 (macrocytosis hyperchromia aniso poikilocytosis)

In the same month the urine was acid with a specific gravity of 1012 there was a trace of albumin but no Bence Jones protein Microscopic examination revealed hyaline and cellular casts and leucocytes

On February 12 the blood count was haemoglobin 42 per cent erythrocytes 2 160 000 per c mm of blood colour index 0 98 leucocytes 6 900 per c mm Total protein in the blood 6 2 per cent

By March 1944 his condition had not altered much there was further loss of flesh in spite of a diet high in calories On March 15 the blood count was haemoglobin 52 per cent leucocytes 6 100 per c mm of blood The differential count (per cent) was neutrophils 47 neutrophils stab 2 neutrophils juv 1 lymphocytes 47 monocytes 3

The leucocytes showed toxic granulation and the erythrocytes hypochromia with anisocytosis The blood urea was 65 4 mg per c c

Radiographs were taken of the thorax spine pelvis and femur all bones were shell like and showed advanced changes There was spontaneous fracture of one rib and gross changes were noted in the skeleton of the chest wall

Repeated examination showed a trace of albumin in the urine but no Bence Jones protein

On May 25 1944 the blood count was haemoglobin 46 per cent erythrocytes 2 680 000 per c mm of blood colour index 0 80 leucocytes 7 100 per c mm The differential count (per cent) was



FIG 3—Section of vertebral body an area from which the marrow cells have disappeared completely leaving a thin areolar tissue × 180

3 760 000 per c mm colour index 0 93 leucocytes 9 600 per c mm The blood calcium was 9 5 mg per 100 c c

Radiographic examination of the spine was performed by Dr Roth who found partial collapse of the tenth dorsal vertebra and osteoporosis of the vertebral column The skull showed marks of the previous operation

In December 1943 the patient had a spell of partial mental disorientation and drowsiness lasting for two weeks On December 6 the urine showed no trace of albumin or sugar the blood urea was

(with gelatinous bone marrow) the sternum with the whole front of the chest and the calvarium Unfortunately the pituitary gland was lost

Dr Greenfield s Histological (Amended) Report

Spleen —In the spleen there was thickening both of the fibrous tissue septa and of the adventitia of the blood vessels No Malpighian bodies were seen The arterioles were thick walled but without hyaline change in the media There was diffuse fibrosis of the pulp and a very large amount of blood pigment collected in masses or in smaller intracellular collections There was a diffuse increase in the numbers of lymphocytes and plasma cells in the sinus system

Liver —The liver cells also contained a large amount of blood pigment most of which gave the Prussian blue reaction swollen Kupffer cells were also seen full of Prussian blue granules There was also some excess of bile pigment in the liver cells There was no excess of lymphocytes in the portal tracts

Aorta —The aorta was normal The thyroid showed diffuse fibrosis but no evidence of hyperactivity

Kidney —In the kidney there was a diffuse deposition of small calcified knots in the interstitial fibrous tissue both in the cortex and medulla Some small wedges of degeneration and fibrosis were seen passing in from the capsule The smaller arteries showed slight concentric and eccentric thickening of their walls but no hyaline degeneration of the media Some of the glomeruli showed slight hyaline changes

Brain —In the area of the brain from which the tumour had been removed there was softening of the subcortical white matter over a limited area with collagenous and neuroglial scarring calcium deposition in this and the zone immediately surrounding it and the presence of many granular and other phagocytic cells

Prostate —The prostate showed an excess of small calculi (prostatic sand) but no other abnormality

Bones —In the dark areas the skull contained fairly large Haversian canals which were filled chiefly with thin areolar tissue but many contained also rather sparse marrow cells (Gelatinous degeneration of bone marrow) There was some irregularity in the lines of ossification but no evidence of osteoid tissue The vertebral bodies showed extreme osteoporosis only a very thin outer shell of bone remaining with some thin spicules of bone in the medulla Here the marrow cells were in places very sparse and in places absent In the latter areas the connective tissue was of finer character than in the skull

neutrophils 57 lymphocytes 40 *monocytes 1 basophils 2 There was* toxic granulation and aniso-poikilocytosis

Unfortunately the blood which was taken for estimation of *phosphatase and phosphorus was lost* on two occasions and these important data are therefore missing

On August 28 1944 the blood count was haemoglobin 54 per cent erythrocytes 3 240 000 per c mm of blood colour index 0 80 leucocytes 7,300 per c mm The differential count (per cent) was neutrophils 40 lymphocytes 56 promyelocytes 3 plasma cells 1

There was fracture of another rib and the patient was feeling weaker and was much thinner There was temporary corneal erosion much pain when moving and falling in of the sternum He died on September 13 1944

Treatment —Between November 12 1943 and January 19 1944 he had fersolate vitamin D (calciferol) and injections of colloidal calcium In January 1944 a leather jacket was given to him but it was never worn From May 25 1944 radiostoleum and calcium were given by mouth Beginning on June 18 he received twenty injections of colloidal calcium after which from July 20 he had twenty injections of calcium (Sandoz)

On August 25 1944 morphine was started

Necropsy —There was extreme emaciation The organs were pale and very reduced in size and weight the bones of the thoracic cage and vertebral bodies were shell like and there was *osteoporosis of* all bones especially of the spine The bone marrow of one of the iliac bones was examined and found macroscopically to resemble that of the ribs The bone marrow was partly gelatinous The *macroscopic* appearance of the internal organs was normal except for their small size The weight of some of the organs was as follows

		Normal average
Brain	1 250 g	1,358 g
Heart	200 g	300 g
Liver	700 g	1 600 g
Spleen	250 g	250 g
Kidney (left)	150 g	150 g

The following were sent for pathological examination to *Dr J G* Greenfield at the Chase Farm Hospital Enfield pieces of spleen liver and aorta the urinary bladder with the prostate gland the thyroid gland a suprarenal gland and the pituitary gland the *left* kidney and brain the greater part of the vertebral column with ribs attached part of the right ileum the central part of the right femur

secondary hyperparathyroidism no excess of blood calcium was discovered

Summary

The case was that of a man aged 44 years who in January 1943 commenced to suffer on and off from pain in the back Signs of severe osteoporosis of the vertebral column and ribs gradually increased and were accompanied by considerable anaemia He died in September 1944 The necropsy showed osteoporosis especially of the vertebral column and chest wall As in similar (though somewhat less extreme) cases recorded in the literature of the subject no cause was discovered and all treatment was unavailing The actual bony collapse was less in the vertebral column than in the thoracic cage where falling in of the sternum was a result

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Discussion

Extreme spinal and thoracic osteoporosis with resulting deformity may as Burrows and Graham (1947) point out be found in known diseases causing *osteoporosis and similar deformities may* as is well known occur in osteomalacia One of us (Parkes Weber 1897) under the heading general lymphadenosis of bones one form of multiple myeloma described the case of a man aged 61 years whose spinal column and thoracic cage were infiltrated and largely replaced by some kind of a malignant very vascular neoplasm The bones and microscopic sections were carefully examined by the late Prof S G Shattock by whom specimens were arranged and described in the *museum of the Royal College of Surgeons in London* (catalogue 2115D 1640E 1640F) No similar case has been met with since then The ribs were all converted into delicate tubes formed of periosteum with only a thin imperfect shell of bone they were stuffed full of the new growth

In regard to the collapse of the front wall of the thoracic cage and the consequent falling in of the sternum one of us (Parkes Weber) has seen a similar appearance in a young man but that was the case fully *described* by Graham and Stansfeld (1946) under *the heading* A Hitherto Undescribed Lipoidosis simulating Rheumatoid Arthritis

Whether cases similar to those described under the heading Milk man s disease are in any way related to idiopathic spinal osteoporosis seems to be answered in the negative by McCance s paper (1947) on Osteomalacia with Looser s nodes (Milkman s Syndrome) due to abnormal resistance to absorption of vitamin D The term Looser s zones is probably preferable *to Looser s nodes*

A question which arises and cannot yet be answered is whether cases of severe or less severe idiopathic spinal osteoporosis are related in any way to the ordinary cases of generalized osteoporosis in old age (Kesson and others 1947) (*See also* Black and others 1941 and Merklen 1936)

As to the cause of the haemolytic anaemia in the present case it seems highly probable that it was in some way connected with if not directly due to the changes in the bone marrow

It is unfortunate that owing to wartime difficulties our data are incomplete with regard to the blood phosphorus the blood phos phatase and histological *examination of the pituitary* and para thyroid glands However it is unlikely that the temporary renal disturbance evidenced especially by high blood urea caused

limited to a single extremity in a female baby aged five months the left leg was uniformly fatter but not longer than the right radiography showed that the bones and muscles of both sides were equal

The relative preponderance of the subcutaneous fat in the buttocks and thighs of women is a sex character and is strikingly illustrated in some cases of so-called lipodystrophia progressiva superior in whom the lack of subcutaneous fat in the upper part of the body is accompanied by an increase of the fat over the buttocks and thighs which makes the fat atrophy still more noticeable by contrast Occasionally it may constitute the main feature of the case (type of Laignel Lavastine – *see* Segmentary Adiposis of the Lower Limbs by Laignel Lavastine and Viard *Nouv Iconographie de la Salpetriere 1912 25 473*)

What one may call bull neck in men is probably analogous to the fatty and muscular prominence (a sex character) on the back of the neck of bulls An extreme and really pathological form of bull neck is the so-called symmetrical diffuse lipomatosis of the nape of the neck (certain other regions may also be affected) It is a rather rare form of constitutional localized dystrophic hypertrophy of the panniculus adiposis which occurs in middle aged men – mostly excessive beer-drinkers who often show a generalized tendency to put on fat women are hardly ever affected (cf F P Weber *Trans Clin Soc Lond* 1904 37 220)[1] It must not be confused with Dercum s disease (adiposis dolorosa) a rare condition seen chiefly in middle aged women which is probably partly of endocrine origin Patches *of inflammatory (probably ischaemic) sclerosis are not rare in diffuse* lipomatosis and Dercum s disease such patches may be painful and tender on pressure and constitute one form of chronic panniculitis

Areas of dysplastic hypoplasia or (rarely) hyperplasia of the sub cutaneous tissue (panniculus adiposus) of congenital or developmental origin constitute a rare kind of naevus in the broad sense of the term But there are also scattered patches of atrophy of sub cutaneous fat or subcutaneous tissue which seem to constitute a condition allied to morphoeic scleroderma the sclerodermatous *patches being represented by atrophic not sclerotic areas in the sub* cutaneous tissue the skin itself not being necessarily involved at all

In regard to dysplastic and dystrophic conditions of the sub-cutaneous tissue one should mention the various forms of

ever be of the kind regarded as representing hibernating pads in animals

[1] I do not know whether fatty lumps at the back of the neck in women may

XXIII

GENERAL AND LOCAL, DYSPLASTIC OR DYSTROPHIC EXCESS OR LACK—AND OTHER DYSPLASIAS—OF THE SUBCUTANEOUS FAT AND SUBCUTANEOUS TISSUE[1]

F PARKES WEBER

THE following is meant as a supplement to my article on Dysplasias and Dystrophies of the Subcutaneous Tissue in *Rare Diseases and some Debatable Subjects*, page 23

General

Among dystrophies one may include hypertrophies and hypotrophies or atrophies I limit the term dysplasia as far as possible to include *only obvious inborn developmental conditions* whether congenital or manifesting themselves during post natal development Although generalized obesity is nearly always a kind of hypertrophic fatty infiltration of the body (especially the subcutaneous tissue) due to over nutrition there is often an obviously dysplastic constitutional factor present This is shown by the fact that some individuals become obese much more readily than others and have great difficulty in warding off excessive obesity by dietetic and other methods To a lesser degree the same may be said of excessive generalized leanness though the cause of the latter condition is almost always to be found in dietetic factors or in the presence of actual disease of organs concerned with the metabolism and the general nutrition of the body

Local

The two halves of the body are seldom perfectly symmetrical Developmental hemi hypertrophy or hemi hyperplasia of various types should be regarded as representing a rare exaggeration of this discrepancy between the two sides Minor degrees may sometimes become less marked as a child grows up The hypertrophy or hyperplasia may in certain cases involve not the bones but only the soft parts Thus cases of hemi obesity have been described by Robert Hutchison (*Rep Soc for Study of Diseases in Children* 1904 4 145 and *Brit Jl Child Dis* 1904 **1** 258) and H Batty Shaw (*Proc Roy Soc Med* 1915 **8** Clinical Section 15) A query in the *Brit Med Jl* (1948 **1,** 284) shows that such hemi obesity may be only partial and

[1]From the *Medical Press* 1948 **219** 238

COMBINED OSSEOUS AND DERMAL DYSPLASIAS—DEVELOPMENTAL OSTEODERMOPATHIES[1]

F PARKES WEBER

Acromegalic and Acromegaloid Cases

E UEHLINGER (*Virchows Arch* 1942 **308** 396 and *Fortschr a d Geb d Roentgenstrahlen* 1943 **67** 8) discusses the Friedreich Erb Arnold Disease – generalized hyperostosis with pachydermia or idiopathic familial generalized osteophytosis N Friedreich (*Virchows Arch* 1868 **43** 83 with Plate I) described the cases of two brothers under the heading of hyperostosis of the whole skeleton The skin of the hands and feet was thickened and there was some general cutis laxa Friedreich thought that the hyperostosis was remaining stationary He referred also to the case of a man (Saucerotte Melanges de Chirurgie Paris 1801 p 407) aged 39 with general hyperostosis including the skull but that case was apparently genuine acromegaly (*see* F R B Atkinson Acromegaly 1932 p 3) W Erb dealt with Friedreich s cases in *Deut Arch klin Med* 1888 **42** 295 and Julius Arnold made the post mortem examination on the elder of the two brothers (*Beitr path Anat* 1891 **10,** 1) He summed up in favour of the diagnosis of acromegaly but the question is still unsettled Pierre Marie regarded the brothers as examples neither of acromegaly nor of secondary hypertrophic osteo-arthropathy (*see* L van Bogaert *Journ de Neurologie et de Psychiatrie* 1928 **28** 502)

There are cases which may be labelled Hereditary acromegaloid conditions of which I suggest that cases of familial clubbed fingers (*see* F Parkes Weber *Brit Med Journ* 1919 **1** 379 and *Medical Press* 1921 **162** 27) are mild varieties[2] G von Pannewitz in his article on acromegaloid osteosis (*Roentgen Praxis* 1935 **7** 682) claims that the case he describes is the seventh recorded example His case has the bulldog type of folded scalp or *cutis verticis sulcata* a rare accompaniment of acromegaly (*see* F Parkes Weber *Brit Journ Derm* 1928 **40** 1 and Atkinson and Weber *ibid* 1928 **40** 454) I have explained what I regard as the most likely relationship of the two conditions (Rare Diseases and Some Debatable Subjects 1946 p 26) in the following way In most typical cases of acromegaly

[1]Enlarged from the *Medical Press* 1949 **221** 55 and from a Communication at the annual meeting of the Assoc Phys Gt Brit and Irel 1949

[2]For reference to more recent cases of Familial Clubbing of Fingers see W P U Jackson *Brit Med Journ* 1949 **1** 216

chalasodermia loose skin (cutis laxa) dermatolysis and hyperelastic skin (cf F P Weber *Urologic and Cutaneous Review*, 1923 27, 407). It seems that in cutis laxa as in hyperelastic skin an atrophic or developmental dysplastic change produces deficiency of the normal attachment of the skin to the deeper structures Cutis laxa is often a striking feature of the Ehlers Danlos syndrome—a peculiar inborn dysplasia mainly of the skin and subcutaneous tissues but is not present in every case and when present may be limited to certain parts of the body notably about the elbows and knees Areas of cutis laxa may likewise be present in the developmental dysplastic disease elastosis dysplastica (elastosis dystrophica of Bock) or as it is still usually termed *pseudoxanthoma elasticum* There is a kind of local cutis laxa due to loose swelling of the subcutaneous tissue which may accompany the early manifestations of some cases of *acanthosis nigricans associated with malignant neoplasms* of abdominal viscera A remarkable kind of dermatolysis is sometimes seen in neurofibromatosis (von Recklinghausen s disease) In *extreme degrees of this dermatolysis of neurofibromatosis* folded hyperplastic masses of subcutaneous tissue and skin hang like flounces or curtains over portions of the body or are suspended from the *abdomen or lower part of the trunk over the thighs* The curious condition of bull dog scalp (cutis verticis gyrata) should be mentioned here It appears to be sometimes due to an excessive local *action of the pituitary growth hormone in acromegaly* the skin and subcutaneous tissue of the enlarged scalp becoming folded in order to keep approximated to the surface of the skull Bull dog scalp is *however in some cases a developmental naevoid dysplastic* condition In certain other cases it might perhaps be compared to bull neck an atavistic dysplastic abnormality of the male sex (*see above*)

In scleroderma and in what I prefer to term the symptomatic sclerodermatous conditions the subcutaneous tissue and sometimes the muscles may be involved but I will not discuss these conditions here

XXIV

COMBINED OSSEOUS AND DERMAL DYSPLASIAS—DEVELOPMENTAL OSTEODERMOPATHIES[1]

F PARKES WEBER

Acromegalic and Acromegaloid Cases

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hypertrophy of parts of the subcutaneous tissue constitutes a conspicuous feature notably in the face hands and feet The excessive production of growth hormone in the anterior part of the pituitary gland which is the cause of acromegaly seems to work differently in different acromegalics – in some the changes are mainly in the bony skeleton in others the soft parts are equally or even more strikingly affected the viscera may be specially enlarged (acromegalic cardiomegaly *gastromegaly etc*) and *in a very few the scalp may be* so hypertrophied in area as well as in thickness that it has to become folded or convoluted to keep attached to the skull Thus acromegaly is one cause of the rare clinical condition known as cutis verticis gyrata cutis verticis sulcata furrowed scalp bulldog scalp whirlpool scalp and megalia cutis capitis (the condition is by no means always limited to the vertex or hairy scalp) other causes being a congenital or developmental naevoid dystrophy and extremely rarely Recklinghausen s neuro fibromatosis

In some cases of furrowed scalp in *acromegaloid* individuals the pituitary fossa may be apparently normal (compare R J Sisson *Journ Amer Med Assn* 1926 **86** 1126 A Gronberg *Act Med Scand* 1927 **67,** 24 and an article in *Arch f Derm u Syph* 1926 **154** 595) It seems that in some individuals there is an inborn tendency *(possibly familial) for local acromegaloid changes to occur* even when the pituitary gland is perfectly normal

On this whole subject one may compare the case described (*Presse medicale* 1935 **43** 1820) by A Tourraine G Solente and L Cole under the heading un syndrome osteo dermato pathique la pachydermie plicaturee avec pachyperiostose des extremites J N Roy of Montreal without knowing of this French case described a very similar case in Canada (*Canadian Med Assoc Journ* 1936 N S **34** 615) under the heading Hypertrophy of the Palpebral Tarsus the Facial Integument and the Extremities of the Limbs associated with Widespread Osteo periostosis (*See also* the reference in *Presse medicale* 1937 **45,** 403) In 1928 Marcel Labbe and Paul Renault had written an article (*Presse medicale* 1928 **36** 545) entitled L osteodermopathie hypertrophiante I have also heard of a case labelled Acropachy published I think in America the patient was a negro in the Johns Hopkins Hospital who after partial thyroidectomy developed a mixture of hypertrophic osteopathy and pachydermia of the extremities A Apitz (*Virchow s Arch* 1940 **305,** 216) wrote on an as yet unrecognized type of clinically harmless generalized *osteosclerosis* to be sharply distinguished from true

marble bones and *osteopoikilosis* but this does not concern us at present as there were no associated dermal features

If I am correct in my views it is obvious that cases of a kind of developmental acropachy may occasionally (very rarely) turn up involving the soft parts of the hands wrists and forearms (or else—or with—an analogous condition in the lower limbs) without any demonstrable change in the bony skeleton (unless perhaps rather unusually *large bones) and without any enlargement of the pituitary* gland I would be inclined to include such a case as possibly one of incomplete *acromegaloid* osteodermopathy involving soft parts only

Other Cases

But besides acromegaloid and true acromegalic cases there are other combined osseous and dermal dysplasias and L Lichtwitz (*Functional Pathology* London 1942 p 311) writes In rats H Selye (*Endocrinology* 1932 **16** 547) has experimentally produced simultaneously with bone changes of the cystic and hyper osteotic type sclerotic processes of the skin very similar to the pathology of scleroderma

The condition of osteopoikilosis or osteopathia condensans disseminata (Wachtel) was well described by Albers Schonberg in 1915 (*Fortschr a d Geb d Roentgenstrahlen* 1915 **23** 174) in a man aged 22 years He had already (1904) discovered the generalized condition of marble bones (osteopetrosis) In osteopoikilosis there are islands of condensed bone consisting of closely packed trabeculae scattered in various parts of the skeleton notably in the pelvis seldom in the skull According to Sir Thomas Fairbank (*Journ Bone and Joint Surg* 1948 **30B** 544) the condition has been observed at all ages from foetal life to over 60 and is always discovered by chance since it produces no symptoms Heredo-familial incidence is sometimes very striking

A Buschke and Helen Ollendorff (*Derm Wochenschr* 1928 **86** 257) described the association of osteopathia condensans disseminata with a doubtless developmental dermatosis which they called dermatofibrosis lenticularis disseminata in a somewhat infantile and weakly woman aged 41 years Ollendorff (Helen Ollendorff Curth) again dealt with this subject in *Arch Derm and Syph* 1934 **30** 557 She concludes Osteopoikilosis and dermatofibrosis lenticularis *disseminata apparently represent two manifestations in* different organs of a similar lesion of the connective tissue In one instance *lesions* of the same type occurred in the peritoneum The disease is probably a hereditary anomaly In a final note she refers

to a discussion on the relationship between osteopoikilosis and scleroderma Von Bermuth (*Zeitschr f Kinderheilk*, 1932 **54**, 103) had described this association in a child Besides the patchy form of osteopoikilosis there is a (longitudinally) striated form first described by N Voorhoeve (*Acta Radiologica*, 1924 **3**, 407)[1] Both forms (inter mediate cases also occur) may be associated with dermatofibrosis lenticularis disseminata (compare A Lindbom *Acta Radiologica*, 1942 **23**, 296) Lindbom s two cases of the striated form were a boy aged 13 and his sister aged 15 In both brother and sister dermatofibrosis lenticularis disseminata was present this observation strengthening the concept that osteopoikilosis in streaks is closely related to osteopoikilosis in spot like patches

For cases of melorheostosis (possibly allied to local or monomelic eburnisation or osteopetrosis) associated with dermal conditions like pachyderma scleroderma or *trophoedema see* G S Hall *Quart Journ Med* 1943 new series **12**, 77–100 In the affected hand of his own case the skin over the ventral surface of the thumb and particularly the forefinger was thick and tightly bound down by dense fibrous bands to the underlying tissues In Lewin and MacLeod s case (1925) the skin over part of the right hand was red indurated and tender the fourth and fifth fingers were swollen and bent In Meisels s case (1928 1929) there was diffuse non pitting thickening of the lower part of the affected thigh the skin of which was tense shiny and adherent to the underlying tissues while there was a diffuse erythema associated with an abnormal distribution of vessels over the region of the hip Meisels thought that these changes corresponded to Meige s trophoedema In Dillehunt and Chuinard s case (1936) – a boy aged 10 years – there was a widespread scleroderma like condition of the thigh of the affected side In Gillespie and Siegling s case (1938) – a girl aged 7 years – the affected (right) lower limb was covered with scleroderma like skin the subcutaneous tissues being apparently also involved Hall says that repeated references are made in the literature on melorheostosis to the changes of the skin and subcutaneous tissues *overlying the bony lesions the frequency* of which changes suggests that they constitute an integral part of the disease Of the nine cases in which they were present they were sufficiently prominent in two (Dillehunt and Chuinard 1936 Gillespie and Siegling 1938) to be mistaken for scleroderma and once (Meisels

[1]It seems that the remarkable case described by Sir Thomas Fairbank in 1925 (*Brit Journ Surg* 12 594) is a unilateral example of Voorhoeve s striated form of osteopoikilosis (without dermal involvement)

1929) for trophoedema Hall continues It is perhaps significant that only the deeper layers of the skin those of mesodermal origin which constitute the dermis proper are affected It is suggested that in the more severe forms of melorheostosis changes occur simultaneously in all the tissues which are affected with the result that they form a suitable medium into which ossification may spread from the nearest local deposit of calcium the adjacent bone One tissue which is affected severely is the periosteum in the local absence of which ossification *overflows* from the bone into the adjacent tissues which with the deeper layers of the skin react by becoming progressively fibrotic and so simulate the appearance of scleroderma

Dr Arthur Elkeles has kindly told me of an unpublished case observed by him a man aged 20 years oxycephalic with definite osteopetrosis He has hardly any hair and his skin is dry and scaly with patches of pigmentation The case has as yet not been completely investigated but it appears to be a combination of a congenital dysplasia of the skin with osteopetrosis involving the whole bony skeleton

Sir Thomas Fairbank (*Journ Bone and Joint Surgery*, 1949 **31B**, 114) in his account of dysplasia epiphysialis punctata (chondrodystrophia calcificans congenita of Hunermann) draws attention to associated thickening of the skin mentioned by some German authors G Miescher described a case of atypical chondrodysplasia associated with follicular atrophoderma (*Dermatologia* 1944 **89** 38) in a girl of 8 years Dr Helen Ollendorff Curth who kindly referred me to Miescher s paper is preparing a paper on this subject and has chosen the descriptive title Follicular atrophoderma pseudopelade and chondrodystrophia calcificans congenita R W B Ellis and S Van Creveld (*Arch Dis Child* 1940 **15** 65) have described a remarkable Chondro-ectodermal dysplasia – a syndrome characterized by Ectodermal Dysplasia Polydactyly Chondrodysplasia and Congenital Morbus Cordis The hair nails and teeth were involved and the condition was held to be a Mendelian recessive without sex linkage Here one may refer also to the paper by H N Cole *et al* headed Ectodermal and Mesodermal Dysplasia with Osseous Involvement (*Arch Derm and Syph* 1941 **44** 773) The patient had congenital absence of the third toe and third metatarsal bone of the left foot syndactyly of the last two fingers of the right hand and nearly complete fusion of the first two digits of the left foot F Parkes Weber (*Brit Journ Child Dis* 1929 **26** 270) had discussed earlier literature in regard to combined ectodermal defects in which there

had been aplasia or hypoplasia of the patellas anomalies of the finger and knee joints and defects of the clavicles Cole and his associates refer also to cases of the same class collected by H A Cockayne (1933) or recorded by others Compare also C I Hawkins s communication (*Assoc Phys Gt Brit and Irel* 1949) on a case (with interesting familial history) of multiple congenital abnormalities including absence or hypoplasia of patellae dysplasia of finger nails and elbow joints bony iliac horns and congenital dysplastic nephritis (cf F P Weber in discussion *Trans Med Soc Lond* 1949 **65** 249) Concerning bony iliac horns Hawkins refers to I I Fong *Radiology* 1946 **47, 517**)

In regard to the subject of combined osseous and dermal dysplasias one must not forget the association of patches of cutaneous pigmentation with polyostotic areas of fibrous or fibrocystic bony dysplasia in Albright s disease In von Recklinghausen s neurofibromatosis bony parts as well as skin and subcutaneous tissue are sometimes involved (compare Weber and Perdrau *Quart Journ Med* 1930 **23, 151**) Sarcoidosis may affect both skin and bones but cannot be included here among developmental dysplasias On the other hand however xanthomatosis of the skin may occasionally be associated with xanthomatosis of bones and xanthomatosis is sometimes certainly developmental and familial for instance xanthelasma palpebrarum in sibs

Perhaps arthropathia psoriatica the well known combination of rheumatoid arthritis with psoriasis—both to some extent familial diseases—might be included here if not as a developmental osteodermopathy at least as a developmental arthro dermopathy

Discussion

It is a well known rule that when one developmental abnormality is present others should always be looked for The frequent association of various kinds of developmental abnormalities or malformations is clearly illustrated in asylums for mentally defective children where the abnormal mental development is found not rarely to be associated with other developmental abnormalities such as mongoloid features congenital heart disease malformations of the extremities etc In this article I have attempted to make a rough classification of the known combinations of osseous and dermal dysplasias. In some groups various other developmental abnormalities are superadded thereby increasing the number of known developmental syndromes

Many developmental diseases and congenital abnormalities almost certainly have a mutational origin and William Bateson the Mendelian investigator of Cambridge proclaimed as a motto Treasure your exceptions On account of their great number and almost endless variety it is very hard to remember and classify developmental exceptions Combined associations may also be increased in variety by intermarriage between two families with different mutational diseases for instance epidermolysis bullosa and Recklinghausen s neurofibromatosis (*see* F Curtius and R Stempel *Derm Zeitschr* 1928 **51** 401)

A FAMILIAL CONDITION RESEMBLING CLUBBED FINGERS[1]

F PARKES WEBER

THE patient B H aged 51 years is a cabinet maker of Russian Hebrew origin He is a well built man who has suffered during the last year from pain and swelling in various joints The blood serum taken on September 30 1920 gave a positive Wassermann reaction but there is no history of syphilis and he is the father of ten children six of whom are living His fingers (and to a less extent his toes) are clubbed and the skin around the finger nails is slightly reddened Roentgen ray examination of the hands shows nothing abnormal in the bones and joints He does not know when his fingers became clubbed I have been able to examine a nephew (son of a brother) of the patient J H aged 29¾ years who has the same peculiarity in regard to the finger tips though in a lesser degree In other respects the nephew appears perfectly normal He served in the Army during the great war and has been recently accepted for life assurance at ordinary (first class) rates He tells me that his father (the brother of B H) has the same type of finger tips and so have his only brother and his three sisters the peculiar shape being most marked in the case of his father

In 1919 I had to examine two (twin) brothers aged 25 years for appointments and for life assurance Both of them showed clubbing of the fingers in both hands The toes were not affected in the same way In one of them (A M K) the thorax was not very well developed but the peculiarity in the fingers was slightly less marked in him than in his rather better developed brother (W H K) Both of them appeared free from any visceral disease A M K had been severely wounded in the left leg during the war but had quite recovered (from the life assurance point of view) I regarded both lives as suitable for insurance at ordinary rates An elder brother aged 30 years had the same peculiarity of the fingers I was informed but I did not myself see him They had no other brothers and no sisters I am not aware if the father (who died at the age of about 56 years) had clubbing of the fingers but the mother (still living) had not [1]

In November 1915 I examined an apparently healthy young Irish man (M J R) aged 25 years The only special point to be noted in

[1]*After the Medical Press* 1921 162 2

regard to his condition was that he had incurved nails with clubbing of the *fingers and toes* on both sides of the body This he said he had had ever since he could remember It was an inherited peculiarity not associated with any thoracic or other disease His father and three of his brothers and one of his sisters were said all to show the same abnormality – at least as far as the fingers were concerned It may be observed that M J R had been accepted in 1909 and 1911 for life assurance at ordinary rates

There is one published record of a familial peculiarity apparently of the same kind Von Eiselsberg [2] in 1911 described a congenital and familial condition of the terminal phalanges in a man aged 35 years resembling clubbed fingers in appearance One of his grandfathers one uncle and one sister were known to show the same condition which Von Eiselsberg suggested might be of a lymphangiomatous nature

I would rather not use the term lymphangiomatous for such cases but would suggest that some of the isolated cases of clubbing of fingers for which no cause can be ascertained may be of the same nature even when a history of familial occurrence of the abnormality is not forthcoming As far back as August 1897 I met with a man aged 46 years who had had typical clubbing of all his fingers – not his toes – ever since he could remember I found no cause for the clubbing He had psoriasis but it was of more recent date than the clubbing [3] S West [4] mentioned the case of a woman aged 50 years who came under treatment because she had swallowed some ammonia by mistake Both her fingers and toes were clubbed No cause could be found for the clubbing which was supposed to have commenced three to four weeks previously If this really was so the case would hardly be placed under the present category West likewise recorded clubbing of fingers and toes in an otherwise apparently healthy medical man aged 38 years In a third case of clubbing he could also find no cause For references to more recent cases of familial clubbing of fingers see the paper by Jackson 1949 [5]

May not the familial condition resembling clubbed fingers with which I am concerned be regarded as one type of familial acromegaloid features ? Similarly minor degrees of facial acromegaloid features may occur as developmental peculiarities without any pituitary or other features to suggest true acromegaly

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XXVI

DYSCHONDROPLASIA (OLLIER) OF THE UPPER RIGHT LIMB WITH OTHER DEVELOPMENTAL ABNORMALITIES[1]

T ANWYL-DAVIES and F PARKES WEBER

DYSCHONDROPLASIA (Ollier) is a developmental abnormality of dysplastic origin affecting the growing ends of long bones including the smaller long bones of the hands and feet In most cases the affection is limited to one extremity or else to the two extremities of one side of the body Of the latter *unilateral* variety of dyschondroplasia



FIG 1 —Dyschondroplasia (Ollier) of the right side in a boy aged 13 years Photograph of the patient (1920) to show the dwarfism and deformity of the right limbs

[1]After the *British Journal of Children's Diseases* 1940 37 110

the case described by F Parkes Weber in 1920 under the heading Unilateral Dwarfism of Limbs connected with Congenital Multiple Chondromata was a typical example (figs 1 to 3)

The normal ossification of cartilage in the affected ends of the bones is hindered so that areas of unossified cartilage remain in the diaphyses (especially the metaphyses) which areas by a kind of tumour like hyperplasia may become very large and in such cases they have been usually regarded as true chondromata Owing to

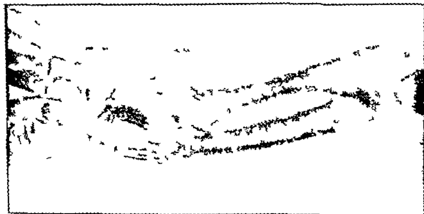


FIG 2 —Same patient as fig 1 Skiagram (1920) of the right forearm to show the chondromata at the distal ends of the radius and ulna there is also a smaller one near the proximal end of the radius



FIG 3 —Same patient as fig 1 Skiagram (1920) of the distal portion of the right leg to show the large chondroma at the lower end of the tibia

the position of these chondromata mostly in the metaphyses close to the epiphyses the growth of the affected limb is generally hindered and shortening of the affected limb or limbs is the rule

The case described by I J Rae in 1936 under the heading Dyschondroplasia with Multiple Chondromata was an extreme example in which all the limbs were affected but the lesions pre dominated on the left side In Cameron and Trethowan s case (1918) the condition was practically limited to the left side J K Monro s case (1935) not unilateral was chiefly remarkable for the enormou size of the chondromata in both hands and also for the fact that the left ulna ended below in a thimble shaped mass of cancellous bone as in some typical cases of multiple exostoses (diaphyseal aclasis of Keith) The latter condition is an analogous developmental dysplasia which as a rule can be sharply separated from dyschondroplasia Donald Hunter and P Wiles whose case is an excellent example of right sided unilateral dyschondroplasia (Ollier) in their paper (1935) give an excellent account of the whole subject with numerous refer ences to the literature including the experience of Sir H A T Fairbank and many others They think that the observations which have been published under the title Systematized Multiple Enchondromata are for the most part records of atypical cases of dyschondroplasia though differing somewhat from the characteristic so called Ollier type

In cases of multiple exostoses (diaphysial aclasis of Keith) there is more frequently evidence of familial and hereditary incidence than in cases of dyschondroplasia

In the family of hereditary deforming dyschondroplasia recorded with a genealogical tree by A G Ord (1925) it should be noted that the radiogram of the right forearm shows that (as in Monro s pre viously mentioned case) the ulna ends below in a thickened mass without reaching the wrist – a local aplastic peculiarity of develop ment well known to be associated not rarely with multiple exostoses (diaphysial aclasis) though rarely with the Ollier type of dys chondroplasia This aplasia (agenesis) or hypoplasia of the distal end of the ulna was well marked in the man with diaphysial aclasis shown by F P Weber at the Royal Society of Medicine on April 11 1924 (figs 4 to 7) it was likewise present in the forearm of the man shown by F P Weber at the same society on February 13 1925 who was apparently free from multiple exostoses and dyschondroplasia (figs 8 9)

As dyschondroplasia and multiple exostoses are conditions both

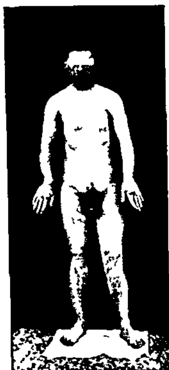


FIG 4 —Diaphysial aclasis (Keith) in an otherwise well developed man aged 23 years Photograph of the patient (1924) to show the deformity of the upper extremities and general good development

belonging to the class of developmental dysplasias it would not be surprising if the two conditions were occasionally found to be associated in the same patient Both conditions probably more often dyschondroplasia may indeed be associated with other developmental abnormalities Thus in the present patient there is not only mental deficiency – some degree of which has often been observed in association with dyschondroplasia – but there is also bilateral epicanthus with thick fleshy upper eyelids somewhat of the so-called ptosis adiposa style Moreover the bad condition of the teeth suggests that there is a developmental defect in the enamel formation

Present Case

The patient Doris T—— aged 10½ has shortening and some deformity of the right upper extremity (*see* fig 10) The thumb

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As dyschondroplasia and multiple exostoses are conditions both

the upper eyelid on both sides internal strabismus and some difficulty in focusing on near objects

Past history and family history —Born in November 1929 one of twins her fellow twin died The Sachs Georgi reaction was negative at birth and both the Wassermann and the Kahn reactions were twice negative in 1939 Measles and whooping-cough at 2 years A

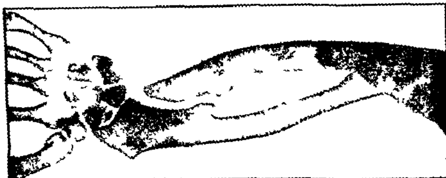


Fig 6—Same patient as fig 4 Skiagram (1934) of right forearm

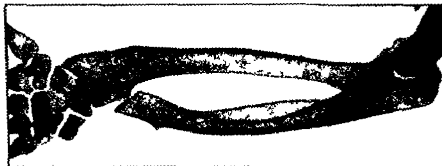


Fig —Same patient as fig 4 Skiagram (1934) of left forearm Apart from the exostoses the chief deformity in forearms and wrists shown in figs 6 and the following, The ulna on both sides owing partly to absence (agenesis) of its distal epiphysis is too short and does not reach down to the wrist so that there is deviation of the hand to the ulnar side This deformity and shortening of the forearm is more marked on the right than on the left side In both forearms the ulna and the radius are slightly bowed with their concave sides towards one another and a striking feature in the skiagrams is the bone formation on the concave (radial) side of the shaft of each ulna as if caused by the interosseous membrane dragging on the periosteum there is also evidence of a little similar bone formation on the concave (ulnar) side of each radius



Fig 5—Same patient as fig 4 Photograph (1924) to show the deformity of the right upper extremity

middle and index fingers are thickened nodular and distorted There is a lump on the lower end of the radius and the upper end of the right humerus which is shortened and bent outwards The lumps are all hard and irregular Radiographic examination shows relatively clear areas in the shaft of the humerus and in the scapula and evidence of a pathological fracture at the upper part of the humerus shaft There are chondromata of the radius thumb and index fingers There is no defect in the bones of any of the other extremities

The girl is somewhat thin but her general bodily development corresponds with her age She is cheerful and obedient but mentally deficient cannot learn to spell and her mother says that though she is willing she cannot help in house work (this is partly however due to the deformity in the right upper limb) Her speech is halting As mentioned above she also has epicanthus and a peculiar fleshiness of

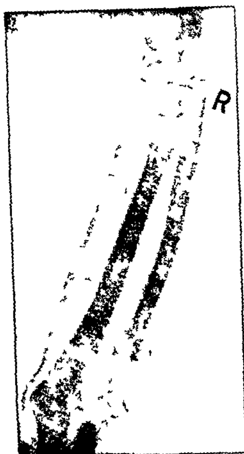


Fig 9 —Same patient as fig 8 Skiagram (1935) showing deficiency of the distal end of the ulna and abnormal separation of the proximal ends of the ulna and radius The patient has neither the multiple exostoses of diaphysial aclasis (Keith) nor the chondromata of dyschondroplasia (Ollier)

normal not mentally deficient At present the mother appears well nourished and her blood Wassermann reaction was completely negative on November 9 1939 But it was strongly positive from 1922 until the birth of the patient in November 1929 during which time she regularly received antisyphilitic treatment at St Thomas s Hospital

Anyhow there is no evidence that the patient had congenital syphilis and there is no certain statistical foundation for the theory that parental (maternal) syphilis can (like an attack of rubella in the



Fig 8—Photograph (1925) of the right forearm of a man aged 18 years showing ulnar deviation of the hand due to a skeletal deformity similar to that sometimes met with in diaphysial aclasis (Keith) and more rarely in dyschondroplasia (Ollier)

swelling appeared in the right thumb two years ago The other swellings have appeared since that on the anterior aspect of the right humerus in January 1939 In January 1939 chondromata were removed from the thumb and index finger but since then they have grown again

The patient s father aged 53 is a bricklayer He has no signs of syphilis and many years ago on three occasions his blood Wassermann reaction was negative but his first wife is said to have died in 1918 of syphilis His first wife had no miscarriages one child now 22 years old is said to be normal and healthy and serving in the Royal Navy

The patient s mother married to the father in November 1920 has had two children and some miscarriages the younger child is the patient the elder is a girl now 13 years old said to be healthy

Weber F Parkes (1920) Unilateral Dwarfism of Limbs connected with Congenital Multiple Chondromata *British Journal of Children's Diseases* 17 85

—— (1924) Diaphysial Aclasis or Periosteo osteo dysplasia (Multiple Exostoses) with Shortness of Forearms *Proc Roy Soc Med* 17 (Clin Section) 40

—— (1925) A Developmental Deformity of the Right Forearm similar to that sometimes met with in cases of Multiple Exostoses (Diaphysial Aclasis of Keith) *Proc Roy Soc Med* 18 (Clin Section) 25

pregnant mother or the application of X rays to the gravid uterus) favour the occurrence of developmental dysplasias and malformations in the children

There is no family history of any other congenital malformation or developmental dysplasia in the family The patient s parents are not related to each other

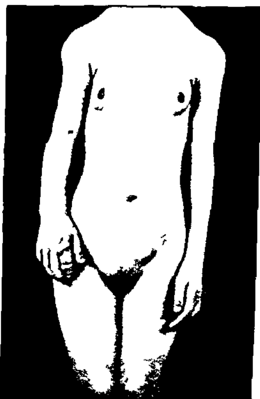


FIG 10 —The present case (girl aged 10½ years 1940) of dyschondroplasia (Ollier) showing shortening and deformity in the right upper limb and notably chondromatous swellings in the right hand (thumb and index fingers)

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Ord A G (1925) *Lancet* 2 178

Rae L J (1936) *Proc Roy Soc Med* 29 1655

(syndactylism) with which indeed congenital cases may be associated

No one as far as I know has ever described any condition of the toes corresponding to camptodactylia of the fingers but contraction of the plantar fascia of the same nature as Dupuytren's contraction of the palmar fascia has occasionally (though rarely) been noted

Rheumatoid ulnar deviation of the fingers may be accompanied by a certain degree of flexion but the flexion is at the metacarpo phalangeal joints

Knuckle pads as described by A E Garrod W Hale White and others are frequently associated with Dupuytren's contraction They are fibrous nodules in the deep cutis and subcutaneous tissue over the extensor surface of the proximal interphalangeal joint of one or usually more fingers easily movable over the bone but fairly closely attached to the skin which is naturally more or less hyperkeratotic over them They vary in size from a split pea to a small hazel nut and are seldom painful or tender or troublesome in any way except for the slight disfiguration which they cause They generally reach their maximum in a few weeks or months They may appear at any age from youth onwards but as they never disappear when once developed they are of course seen more often in old than in young persons there is indeed no special type of senile knuckle pads In one of Garrod's cases they were first noticed at the age of 60 years in another they had already been present for 42 years Two of Garrod's cases had well marked Heberden's nodes in addition to the pads These pads I believe never occur on the thumbs Analogous pads on the toes have apparently been noted They may sometimes be of congenital origin and have been supposed to originate in bursae or bursal rudiments (Compare on the subject of knuckle pads etc F Parkes Weber *Brit Jl Derm* 1938 **50** 26)

Aetiology of Acquired Camptodactylia and Dupuytren's Contraction

Of the existence of a familial tendency in many cases of campto dactylia and Dupuytren's contraction there is abundant proof and that age and the male sex are also predisposing factors in Dupuytren's contraction there can hardly be a doubt But I believe that repeated small traumata constitute the main exciting cause Rowing in the case of university undergraduates seems never to excite Dupuytren's contraction but recommencement of rowing at about 60 years of age

XXVII

A NOTE ON CAMPTODACTYLIA (LANDOUZY) AND DUPUYTREN'S CONTRACTION[1]

F. PARKES WEBER

The term camptodactylia (Greek *kamptos* = bent and *dactylos* = finger) was introduced to the English speaking medical public mainly by an annotation in the *Lancet* of February 22, 1908 (page 579), according to which under that title Professor Landouzy in a clinical lecture at the Charité Hospital in Paris in 1885 and in an article in the *Presse Médicale* in 1906 had described a condition of permanent and irreducible flexion of one or more fingers which developed gradually without pain or inflammation and affected only the inter phalangeal joints, never the metacarpo phalangeal. The right hand was more frequently or (in bilateral cases) predominantly affected. The little finger was usually the only one affected. When more than one finger was involved the fingers affected were the little, ring and middle fingers, only exceptionally the index; the little finger was always the most affected. One or both interphalangeal joints might participate in the flexion, and the interior of the joints themselves seemed not to be structurally involved, further flexion being easy though the hindrance to extension could not be overcome. It was remarkable how little camptodactylia interfered with the use of the hand.

Every doctor would now admit that camptodactylia is intimately allied to Dupuytren's contraction of the palmar fascia, with which in some cases it is associated. It seems to be due to a process of gradual fibrotic contraction of the connective tissue about the sheaths of the flexor tendons in the fingers, in which process the tendon sheaths themselves may possibly be involved. If the connective tissue about the flexor tendon sheaths be regarded as a kind of prolongation of the palmar fascia into the fingers, the analogy and sometimes the actual association with Dupuytren's contraction becomes very intelligible.

But before proceeding further I want to emphasize that I am discussing only *acquired* camptodactylia and Dupuytren's contraction. The so called *congenital* cases of camptodactylia I regard as developmental abnormalities, analogous to other developmental abnormalities of the extremities, such as webbing of the fingers

[1]From the *Medical Press*, 1947, 217, 453.

XXVIII

HYPERTROPHIC OSTEOPATHY ASSOCIATED WITH HEART DISEASE

F PARKES WEBER

THE typical Pierre Marie type of hypertrophic osteo arthropathy is usually secondary to chronic suppuration or neoplastic growth in the thorax A remarkably good example of this type was the case I described (*Proc Roy Soc Med* 1909 2 Clin Section 66–86) under the heading Mediastinal Form of Lymphadenoma (Hodgkin s Disease) with Extreme so-called Pulmonary Hypertrophic Osteo Arthropathy In this type the bone changes tend to be symmetrical and the sub-periosteal new bone formation is well marked encircling the diaphyses especially of the phalanges and metatarsal and metacarpal bones The joints are more often involved in this type than in the following type to which I wish especially to refer and which I would call hypertrophic osteopathy rather than osteo arthropathy

This second (rare) type is associated with (if not secondary to) heart disease (mostly congenital) and chronic pulmonary congestion The bone changes are not always symmetrical and consist in focal periosteal thickenings and sometimes excrescences or exostoses The joints are I believe not involved and the condition as mentioned above might be termed osteopathy rather than osteo-arthropathy The lower limbs are probably mainly involved On this second type *see especially* L F Barker *International Clinics* 1930 3 54 Chronic cyanosis with erythrocytosis in a patient with congenital disease of the heart who also showed signs of toxic osteo periostitis The patient was a woman aged 26 years in whom X ray examination showed multiple exostoses (for instance on left foot and left humerus) and localized periosteal thickenings especially at distal ends of tibia and fibula on both sides *See also* H Batty Shaw and S Melville (*Proc Roy Soc Med* 1917 10 Clin Section 8) and H Batty Shaw and R H Cooper (*Trans Clin Soc Lond* 1907 40 259) Both Batty Shaw s patients had congenital heart disease Compare also the case shown by E Montuschi and G Melton at the Clinical Section of the Royal Society of Medicine on November 14 1947 The skiagrams showed curious periosteal thickenings (and at least one regular exostosis') in the right leg the left leg was not similarly affected The patient was a woman aged 58 years with

may promptly be followed by the appearance of the first stage of Dupuytren's contraction with palmar nodules at first slightly reddish and itchy—a kind of Dupuytren's contraction without as yet any obvious flexion (*see* F P Weber *Med Press* 1923 **166** 133) Similarly the habit of carrying a rather heavy attache case in late middle age may certainly excite camptodactylia if temporary slight pain and a sensation of deep itching in the flexor aspect of the little finger be neglected as warning signs If the attache case has been usually held in the left hand the camptodactylia will commence in the left little finger instead of as it more often does in the right one

In fact I am tempted to suggest that such repeated slight traumata cause the local formation of some chemical substance comparable with *histamine and that in certain hypersensitive* individuals (the hypersensitiveness being connected with their age and family disposition and in Dupuytren's contraction with the male sex) this hypothetical substance sets up a process of local fibrotic reaction—often accompanied by sensations of local deep itching—manifesting itself at length by permanent contraction

Perhaps there may be other contributive causative factors I once saw a man in his eighty ninth year who had recently developed typical Dupuytren's contraction in both hands during his slow recovery from an attack of influenza with bronchopneumonia

XXIX

AMYOPLASIA CONGENITA

(Dysmyoplasia or Myodysplasia Congenita Multiple Congenital Articular Rigidity, Arthrogryposis Multiplex Congenita or Myodystrophia Foetalis Deformans)[1]

F PARKES WEBER

DYSPLASTIC abnormalities of bodily development and (or associated with) developmental abnormalities of bodily functions (tissues organs systems) make up the majority of the various types of rare diseases By their great variety and innumerable combinations they almost defy classification In fact some of the recorded combinations remain unique Yet when a developmental abnormality or rather a combination of developmental abnormalities seems not to fit into the recognized classification the classification must be enlarged or modified so as to include it—for practical purposes of discussion teaching diagnosis and treatment (if any)

The rare dysplastic developmental disease amyoplasia congenita in particular occurs in widely different forms and degrees and in combination with various other developmental abnormalities or syndromes

W Sheldon (1932) in his paper on Amyoplasia Congenita [1] recorded the case of a child aged 2 years with congenitally rigid arms and legs associated with aplasia of certain muscle groups Sheldon stated that under the names multiple congenital articular rigidity and arthrogryposis multiplex congenita a rare but well defined clinical condition had been described the characteristic features consisting of immobility of one or more joints of the limbs generally symmetrical in distribution and dating from intra uterine life The immobility may be absolute or movement may be severely limited The fixation of the joints has the clinical appearance of fibrous ankylosis but there is no evidence of inflammatory change to account for this and it would appear more probable that the condition depends primarily upon some developmental defect In this connection the incomplete development or even entire failure of development of certain groups of muscles in the limbs which has been recorded in cases specifically examined from this point of view has been a striking feature

In the case recorded by Sheldon the condition was of prenatal

[1]From the *Medical Press* 1947 218 593

splenomegalic polycythaemia of the true Vaquez Osler type but with high blood pressure as in the Gaisbock type and hypertensive heart disease with chronic pulmonary congestion She was said to have had an erythromelalgia like condition in the right leg which had already practically subsided (*Proc Roy Soc Med* 1948 **41** 101)

In conclusion I would suggest that when any form of osseous dysplasia is found to be associated with congenital heart disease usually only one limb is affected The bone dysplasia in such cases I would further suggest is really a variant (usually mild) of melorheostosis or else what may be termed *monomelic osteopetrosis* (monomelic bone eburnisation) which is obviously allied to monomelic rheostosis and is a developmental condition

I would add Congenital malformations of the heart (and great arterial trunks) may be associated with mongolism and various other developmental defects and might therefore possibly be associated with developmental – probably monomelic – bone dysplasias I have not heard of congenital bone dysplasias of this type being due to rubella or other infection of the mother during pregnancy which is now an acknowledged cause of congenital heart disease in the offspring

to Embryonic Mortality [3] Greig wrote to me In addition to cranial and facial deformities there are included congenital malformed limbs thickened and flattened tarsometatarsus unilateral absence of muscles and absence of one or two toes The joints are bent on account of the muscular anomalies and many (? unique) cases of twisted feet and toes are mentioned as occurring but are not described Greig himself had seen the chicks and had no doubt of the congenital distortions of the limbs

Sheldon (loc cit) refers especially to H L Rocher s comprehensive paper of 1913 [4] The condition does not appear to affect particularly first born children and from the family histories there is no hereditary or familial tendency Rocher directs attention to abnormalities of the hands and feet notably flexion of the fingers and claw hand and club-foot shortening of the flexor tendons of the fingers has been recorded as in Volkmann s ischaemic contracture flexion of the fingers being more easily performed when the wrists are also flexed The patella is often abnormal being displaced small or even absent The muscles never show a reaction of degeneration so that the muscular atrophy is probably not of nervous origin but the reactions to faradism and galvanism are diminished or absent indicating hypoplasia or complete aplasia of muscle There are no sensory or trophic changes The tendon reflexes are naturally difficult to obtain but when present they are not increased The children are of normal intelligence Rocher drew attention also to the thickened appearance of the subcutaneous tissue obliterating the normal bony markings in parts of limbs but in a case recorded by F Magnus (1903) [5] this subcutaneous thickening was absent and the muscular aplasia was so great that the child appeared to be simply skin and bone Rocher stated that there might be some shortening of the affected limb or segment of a limb Amongst associated conditions there might be ankylosis of the mandible and some vertebral stiffness or scoliosis In a later paper (with C Ouary 1930 [6]) Rocher records the case of a girl aged 3 months with fixation of the legs in extension and double talipes associated with several malformations of the lumbar vertebrae and aplasia of the sacrum According to Rocher there may be abnormality of the synovio-capsular arrangement of joints

A Moncrieff and P Wiles (1934) [7] write that D S Middleton has drawn attention to the resemblance of amyoplasia congenita to a sporadic disease occurring in sheep Should the two prove to be identical it will be of great interest because Fraser Roberts has been

origin bilateral and symmetrical There was extension of the elbow and knees and limitation of movement in the shoulders wrists and ankles inability to pronate the forearms and bilateral talipes equinus There was great diminution of some muscle groups in the limbs and complete absence of others the affected muscles being those which should normally have carried out the movements in which the child was deficient

Sheldon reviewed the literature of the subject collecting 44 cases the case he himself described and four cases under the care of Sir Thomas Fairbank bringing the *total number of cases up to* 49 From his discussion of the pathogenesis he came to the conclusion that the name *amyoplasia congenita was preferable to multiple* congenital articular rigidity and arthrogryposis multiplex congenita *He thought that the most likely explanation was to regard the initial* defect as a developmental aplasia or dysplasia of certain groups of limb muscles secondary developmental changes occurring in and around the joints leading to the clinical picture of fibrous ankylosis This does not signify (I would point out) that congenital abnormalities may not sometimes be caused by faulty position folds bands etc *in utero*

D S Middleton (1934) in his Studies on Prenatal Lesions of Striated Muscle as a cause of Congenital Deformity [2] prefers to call the condition myodystrophia foetalis deformans He draws an analogy between it and the muscular dystrophies of post natal life He says it was first described by A G Otto in a book published in 1841

Personally I owe my first acquaintance with cases of this kind to Sir Heneage Ogilvie who in 1929 had a series of affected children under his care at St Vincent s Orthopaedic Hospital (Eastcote Pinner) On June 17 1929 he and the resident medical officer F J Lees showed me two of the five cases but Sir Heneage tells me that they have never been published and has kindly given me permission to refer to them The evidence of the occurrence of other developmental abnormalities in children of the series was noteworthy Thus in one of the female cases there was a urachus abnormality the urinary bladder reaching nearly up to the umbilicus One of the cases had a brother or sister affected with a meningocele or encephalocele and another seems to have had a fellow sib with cleft palate

D M Greig of Edinburgh kindly directed my attention (1929) to investigations by F B Hutt and A W Greenwood Studies in Embryonic Mortality in the Fowl III – Chick Monsters in Relation

Is there a condition of developmental dysplasia of subcutaneous tissue analogous to and sometimes associated with aplasia or dysplasia of striped muscles (amyoplasia or dysmyoplasia congenita)?

For the question of the relation of amyoplasia congenita to congenital tibial kyphosis (congenital angulation of the tibia) and to congenital high shoulder (congenital elevation of the scapula Sprengel s shoulder) *see* D S Middleton s Studies on Prenatal Lesions of Striated Muscle as a cause of Congenital Deformities (quoted above) [13]

The consideration of amyoplasia (dysmyoplasia) congenita suggests a classification of developmental diseases and syndromes into primary or central developmental abnormalities with secondary features and associated developmental abnormalities grouped around the primary abnormality of development Thus if amyoplasia (dysmyoplasia) congenita be regarded as a primary or central condition the accompanying multiple arthrogryposis may be taken as a secondary feature in so far as it is due to a kind of atrophy or sclerotic shrinkage of the affected muscles or to the same primary dysplastic process involving periarticular connective tissue and even the joints themselves as well as muscles The frequent presence of various other developmental abnormalities can be explained by the well known fact that when one abnormality in development is present various other abnormalities in development sometimes of a quite different kind can not infrequently be detected when looked for

Can the remarkable case described as Myositis Fibrosa by F E Batten (1904) [14] be regarded as an allied (very rare if not unique) condition of delayed developmental dysmyoplasia – in spite of the freedom of the hands and legs? According to Batten s description the patient a boy the second of five children was healthy till 9 months old when the mother noticed that the back became curved and the legs drawn up The condition steadily progressed so that at 6 years old he was rigidly fixed in a flexed position the right sternomastoid muscle being greatly contracted No evidence of disease of the nervous system could be detected The boy died when 6 years old Necropsy showed extensive contraction of muscles especially the right sternomastoid and the recti abdominis and these muscles were of cartilaginous hardness Microscopic examination revealed a general interstitial fibrosis of all muscles examined Batten himself regarded the case as one of primary fibrous myositis and closely related to myositis ossificans

able to show by selective breeding that in sheep the condition depends upon the homozygous state of an autosomal recessive factor

L M Edwards (1938) in demonstrating an infant with webbing of lower limbs associated with congenital bilateral contractions of flexor muscles of elbow and wrist [8] which I suppose to be allied to amyoplasia congenita refers to the question of such webbing representing an atavism analogous to the webbed wing of a bat Similar folds are seen in the neck of the chimpanzee Bruns and Kredel he says maintain that the *condition of webbing owes its origin to misplaced* and abnormal muscular developments bridging the flexor surfaces of joints and displacing the overlying skin in web-like formation Traces of muscular tissue are often encountered between these skin folds

In regard to associated developmental abnormalities a very interesting case has been described by R N Herson (1947) [9] The patient is a woman aged 61 years who in addition to the amyoplasia congenita has a condition of hyperostosis frontalis interna and has been *subject to headache as long as she can remember* A much more complicated case is that of a boy aged 14 years demonstrated by Dr Denis Williams at the Neurological Section of the Royal Society of Medicine on October 2 1947 In his case there is maldevelopment of the osseous muscular and subcutaneous tissue with central nervous system dysfunction

A number of questions arise from the consideration of amyoplasia (dysmyoplasia) congenita

Perhaps some abnormalities of the hands such as congenital camptodactylia with or without webbing (compare Parkes Weber 1938 [10] and 1947 [11]) might be regarded as minor varieties of amyoplasia congenita I would instance especially the case of a man aged 47 years with developmental camptodactylia of both little fingers and considerable atrophy or more probably hypoplasia of the intrinsic muscles of the hands who likewise has had a kind of facial telangiectasia of the Rendu Osler type for as long as he can remember (Parkes Weber 1938 [12])

Should the term amyoplasia congenita be used to include cases of localized muscular aplasia of the whole or part of the pectoralis major muscle of certain muscles of the abdominal wall of bigger congenital defects of the thoracic or abdominal walls and of fibrous dysplasia of a sternomastoid muscle?

May not some post natal cases of local muscular dystrophy be regarded as *representing* a deferred amyoplasia (dysmyoplasia) congenita?

HEREDITARY LARGE PARIETAL FORAMINA INCLUDING REMARKS ON SYMMETRICAL THINNESS OF THE PARIETAL BONES[1]

F PARKES WEBER and E SCHWARZ

V B a well grown boy aged 5 years The two foramina in the skull (*see* radiograms fig 1 *a* and *b*) are situated one on each side of the sagittal suture about 30 mm from the lambdoid suture The right foramen measures 20 by 25 mm in diameter and is 9 mm distant from the sagittal suture whilst the left one is 15 by 30 mm in diameter and immediately adjoins the suture



Fig 1 (*a*) —V B



Fig 1 (*b*) —V B

This developmental abnormality has been very fully discussed by D M Greig (*Edin Med Journ* 1927 new series 34 629)

In the present child the large parietal foramina are hereditary The boy s mother (also shown) Mrs F B aged 30 years healthy looking not a blood relative of the father has similar large parietal foramina which can be felt and demonstrated by X rays (*see* radiograms fig 2 *a* and *b*) They are 8 by 14 mm in diameter symmetrically situated 18 mm from each other one on each side of the sagittal suture and 25 mm from the lamboid suture The mother like her son has never experienced any inconvenience from them

[1]From the *Proc Roy Soc Med* 1935 29 127

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[13] Middleton D S (1934) *Edinb Med Jl* 41 401
[14] Batten F F (1904) *Trans Clin Soc Lond* 37 12

Fig 3 (*b*)—E S

Neither the father nor their only other child (a boy aged 1 year 9 months) has similar foramina

A sister E S of the boy s mother aged 22 years unmarried (not brought to the meeting) also has large parietal foramina (*see* radiograms fig 3 *a* and *b*) The right one is 11 × 19 mm in diameter and the left one is 9 × 20 mm They are symmetrically situated 15 mm apart and at equal distances from the sagittal suture the upper part of the lambdoid suture cannot be seen in the radiogram

E S has a twin sister said not closely to resemble her and not to show large parietal foramina Their two brothers (aged 28 and 25 years respectively) and their other two sisters (aged 34 and 17 years respectively) and their mother (aged 56 years) and maternal grand mother (living aged 68 years) are said also to be free from the depressions which mark large parietal foramina The husbands of the last two are dead but did not show the typical depressions on their skulls

♂ = ♀
♂ = ♀
♂ = ♀ ♂ = ♀ ♂ ♂ = ♀ ♀ ♀ ♀
Twins
♂ ♂ ♂ ♀



FIG 2 (*a*) —Mrs F B

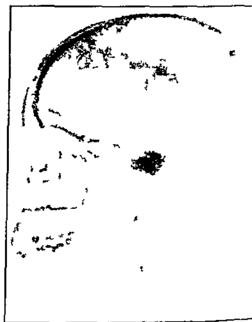


FIG 2 (*b*) —Mrs F B



FIG 3 (*a*) —L S

The defects in the skulls of children due to lipoid granulomatosis of the type of the Hand Schuller Christian syndrome are not likely to be confused with either of the preceding kinds of defects in the parietal bones

Remarks

Large parietal foramina are not always bilateral as is proved by cases of Lancisi Humphry and others referred to by A J E Cave (*Journ Anat* 1928 **63**, 172) In addition to a pair of large parietal foramina a skull *figured by Greig (loc cit)* shows also a large foramen in the occipital bone Large parietal foramina give rise to no clinical symptoms unless forcibly pressed on but that they can be used successfully *for purposes of malingering one case recorded by Greig* proves

Greig (loc cit) seems to have been the first actually to observe *large parietal foramina* in more than one member of the same family His cases were in two brothers But he writes that in W S Symmers s case (1895) the father was *said* to have had the same abnormality *which according to A Macieszа (1910) was likewise found in two* skulls unearthed from the same grave

Large parietal foramina must be distinguished from Symmetrical *Thinness of the Parietal Bones (D M Greig ibid 1926* **33**, *645) due* to abnormal post natal dysplasia abiotrophy or non development of the diploe of the thin areas In the Hunterian Museum of the Royal *College of Surgeons (No 23 F) is a calvarium showing large ovoid* sharply defined symmetrical areas of extreme thinness of the parietal bones This skull is from the necropsy on a case described by F Parkes Weber in the *British Medical Journal* for 1896 **1**, 1027 he discussed the condition of the skull in greater detail in *Brit Med Journ*, 1905 **1**, 129 normal parietal foramina were present and quite separate from the thin areas Next to this skull in the Hunterian Museum is an ancient Egyptian one (presented by Sir Flinders Petrie) with similar parietal depressions also showing normal parietal foramina in the ordinary position Similar depressions in the skull of Khati an Egyptian official of about 2600 B C are described in the *British Museum Guide to the First and Second Egyptian Rooms* second edition p 55) as having been artificially made in early life because the surface of the bones is not broken G M Humphry thought the condition was probably congenital Maier and others considered it a senile atrophy Elliot Smith suggested that it was due (amongst the Egyptians) to the constant *pressure of a heavy wig* Parkes Weber suggests that it is analogous to the remarkable local abiotrophy of the skin on the back of the hands in some old persons *which* G L Cheatle (*Brit Med Journ* 1909 **1**, 1411) proposed to call Biotripsis

blasts (megaloblasts) The erythroblasts superficially resemble large lymphocytes and the basophil normoblasts resemble small lymphocytes – an appearance which led Sanger (Ueber Leukamie bei Schwangeren und angeborene Leukamie *Arch f Gynak* 1888 **33,** 161) originally to regard the disease as a lymphatic leukaemia

Such enormous haemopoiesis in the liver of a non syphilitic infant can only be due to erythroblastosis In this type (i e dying shortly before during or shortly after birth) it is usually associated with general oedema and ascites but in some of my cases these have been quite inconspicuous Several cases of hydrops foetalis have been described with various abnormalities of the genito urinary tract but as far as can be judged the association is quite accidental [1]

Mr Fardley Holland told us that he had never before heard of such a remarkable combination of abnormalities but it could of course occur In regard to the genito-urinary malformation he referred us to A Clinical Manual of Malformations and Congenital Diseases of the Foetus by R Birnbaum English translation by G Blacker 1912 p 211

Patency of the posterior bladder wall is very uncommon In such a case there is a communication between the bladder and the peritoneum or the vagina (fistula vesico vaginalis congenita) or with the rectum (fistula recto vaginalis cloaca) At the same time atresia ani and atresia urethrae may occur

[1]Needless to say any kind of congenital or developmental abnormality is often associated with other kinds

XXXI

CONGENITAL VESICO VAGINAL FISTULA WITH IMPERFORATE HYMEN, HYDROPS FOETALIS AND ERYTHROBLASTOSIS POLYDACTYLY[1]

F PARKES WEBER and M SCHOLTZ

THE subject of this communication was a female child born at the 36th week of pregnancy with very large abdomen and slight general oedema especially noticeable in the extremities and vulva (labia majora) She died a few minutes after birth There was likewise polydactyly – six fingers on each hand six toes on one foot and five on the other There was no jaundice A differential count made from blood taken after death from a subcutaneous vein showed the presence of erythroblasts in the proportion of 113 normoblasts and 8 megaloblasts to 50 leucocytes There was no history to suggest inherited syphilis and the mother s blood gave negative Wassermann and Meinicke reactions The father and mother were apparently normal and this was the mother s first pregnancy There was no family history of polydactyly or of other abnormalities

The *necropsy* showed that the large size of the abdomen was due to great distension of the cavity of the uterus and vagina with urine owing to the presence of a minute vesico-vaginal fistula and imper forate hymen The urinary bladder was empty and a probe could be passed through the urethra into the bladder There was no actual ascites though the abdominal viscera were slightly adherent as if by a gummy substance The spleen was certainly not much enlarged but the liver was big and red on section and weighed 200 grammes The thoracic viscera and brain were not examined The fistulous opening in the wall of the urinary bladder was situated in the posterior middle line close to the urethra the communication was probably valvular as the bladder was empty at the post mortem examination

Microscopic sections of the liver showed a remarkable more or less intercellular permeation with nucleated blood cells Dr J R Gilmour of the Pathological Institute of the London Hospital who kindly examined microscopical sections has sent us the following report

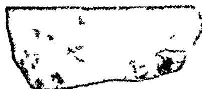
The haemopoiesis in the liver is almost entirely erythropoietic with haemocytoblasts (myeloblasts) erythroblasts basophil and orthochromatic normoblasts ortho and polychromatic erythro

[1]From the *British Journal of Children s Diseases* 1939 36 131

cachectic and obviously ill developed considerable fever and left sided purulent otorrhoea The blood count on January 13 was haemoglobin 60 per cent erythrocytes 4 380 000 per c mm colour index 0 7 white cells 16,550 (myelocytes 4 per cent metamyelocytes 10 per cent polymorphonuclear neutrophils 36 per cent lymphocytes 45 per cent monocytes 4 per cent) The pyrexia continued and the child died on January 24



Inferior surface of the liver showing melanotic tumours



Lower portion of the upper surface of the right lobe of the liver showing the melanotic tumours felt during life

We may say here that the child s urine throughout whenever examined was clear and of a golden brown colour sometimes deeper than at other times It was free from albumin sugar indican acetone diacetic acid and excess of urobilin or urobilinogen The colour deepened when the urine was kept but never became blackish Only on one occasion (January 1) was a supposed positive reaction for melanogen obtained – that is to say on using the potassium nitroprussiate (Legal s) test for acetone we obtained a *deep* green coloration on addition of the glacial acetic acid but this test is of doubtful value

XXXII

SPONTANEOUS INTRA UTERINE INOCULATION OF MELANOMA FROM MOTHER TO FOETUS

Report of a Case[1]

F PARKES WEBER E SCHWARZ and R HELLENSCHMIED

The following is the first and as yet the only reported case of intra uterine transmission of a malignant neoplasm from mother to child by spontaneous inoculation

The child B M aged 8 months a well-developed boy of normal size was admitted to the German Hospital on November 19 1929 The patient s mother (D M aged 27) had died at the German Hospital on July 4 1929 of melanotic sarcoma with visceral and subcutaneous metastases There was no post mortem examination but she was known to have been suffering from melanotic sarcoma for a long time previously Eighteen months ago she had undergone operation at the London Hospital for melanotic sarcoma of the thigh The child was delivered on April 9 by Caesarean section at full term at the London Hospital and was thought to be quite normal at birth Development seemed to be satisfactory till recently when enlargement of the abdomen and a somewhat cachectic appearance of the skin was noted

On admission to the German Hospital the liver was found to be enlarged reaching down to the umbilical level and some large hard rounded nodules could be felt projecting on its anterior surface suggesting malignant neoplasm The spleen was likewise but evenly enlarged its lower border (on palpation) being three fingerbreadths below the costal margin Otherwise the child seemed fairly healthy and quite lively and happy at first excepting that at times there was moderate fever Nevertheless after some time the child began to show increasing cachexia The Wassermann and Meinicke reactions were negative and so was Pirquet s cutireaction for tuberculosis The blood count (November 22) was haemoglobin 76 per cent erythrocytes 4 680 000 per c mm of blood colour index 0 81 white cells 12 400 (polymorphonuclear neutrophils 32 per cent lymphocytes 57 per cent monocytes 10 per cent eosinophils 1 per cent) nothing abnormal was noted in the appearance of the red cells

The liver and the bosses on it probably increased somewhat in size but certainly only very slowly About the middle of January 1930 the child who was gradually losing in weight and becoming more

[1]After the *British Medical Journal* (1930) 1 537

child died at 10¼ months of age minute nodules having developed beneath the skin shortly before death The post mortem examination showed that the bosses which had been felt in the liver were melanotic tumours The size of the growths suggested that the primary infection was in the liver but there were many infiltrated lymphatic glands in the abdomen and minute metastases in the lungs and in the subcutaneous tissue Palpation during life and examination after death pointed to the growth of the neoplasm in the liver having been rather circumscribed and slow as if there was considerable resistance on the part of the child s tissues The tumour cells from which the growths in the child s liver had developed had evidently been carried to the hepatic capillaries (via the blood stream in the umbilical vein) from the placenta which is known to have been melanomatous

The splenomegaly noted by us in the child may be compared to that which has been occasionally known to be associated with hydatid disease of the liver The spleen of infants and children becomes readily enlarged from any toxic or distending cause Thus the spleen was enlarged in a boy with hydatid disease of the liver shown by A F Voelcker at the Medical Society of London in November 1907 A certain amount of splenomegaly was still present in February 1909 after successful treatment by drainage of the hydatid cyst when Dr Voelcker again showed the case [1] In our case the following note kindly given us by Mr Eardley Holland who performed the Caesarean section on the mother at the London Hospital makes it certain that melanotic tumour cells must have passed from the mother through the placenta (owing to actual melanotic metastases in the placenta) into the foetal blood stream The blood in the umbilical vein having chiefly to circulate through the liver some of the melanotic cells were caught up in the hepatic capillaries and these cells were the parents of the multiple melanotic tumours (the primary tumours as far as the child was concerned) some of which could be palpated in the enlarged liver when the child was eight months old

This is the note by Mr Eardley Holland who is going to publish separately an account of the case from the obstetrical and gynaecological point of view

I saw the mother in consultation with her doctor on April 5 1929 She was an ill woman in about the thirty-eighth week of pregnancy with multiple melanotic nodules scattered liberally beneath the skin

Necropsy (January 25) – There were several minute subcutaneous melanotic nodules scattered over the front and back of the thorax of the emaciated child The liver was enlarged (weighing 455 grammes after being kept for some days in alcohol) and several melanotic rounded tumours (up to the size of a pigeon s egg) projected under the capsule notably those that had been palpated during life in front of the liver The spleen was moderately enlarged (weighing 100 grammes) but was otherwise not abnormal in appearance There were a few minute subpleural melanotic patches in the lungs and some small melanotic nodules were attached to the periosteum at the back of the anterior wall of the thorax Many of the abdominal lymphatic glands showed melanotic infiltration one or two of these glands were adherent to the kidneys and pancreas Otherwise macroscopically the viscera appeared normal We were not permitted to examine the head and central nervous system

Microscopical examination – The melanotic tumour cells were typical in all the pieces of growth The small nodule in the liver which we examined was found to be surrounded by a kind of spurious capsule due to compression of the neighbouring tissue and suggesting that the tumour growth had not been very rapid but there were also melanotic tumour cells outside this spurious capsule and many of the Kupffer Sternzellen in the neighbourhood contained melanin granules A piece of lung showed minute bronchopneumonic areas as well as a minute subpleural melanotic growth A tiny subcutaneous nodule appeared to be encapsuled by the distended wall of a capillary blood vessel Pieces of pancreas and kidney showed nothing abnormal but a small lymphatic gland adjacent to the pancreas was infiltrated with the melanotic growth A lymphatic gland removed from the right inguinal region was free from melanotic growth and so was the piece of spleen examined The slight splenomegaly was apparently due to increase of the splenic pulp The Malpighian follicles of the spleen were not large and contained very little germ-centre

Remarks

The main facts of the case may be shortly stated as follows A woman known to be suffering from melanotic sarcoma was delivered three months before her death of a child who appeared at first to be healthy When 8 months old the child was admitted to hospital with an enlarged liver on which bosses could be distinguished by palpation suggesting a malignant neoplasm With increasing cachexia the

were disseminated in that way exhibited a predilection for a limited number of sites

In regard to the last mentioned metastatic predilection we might add that the author did not refer to the wonderful examples of the predilection in human pathology of metastases from *particular* tumours for *particular* sites—for instance the predilection of metastases from the Hutchison type of suprarenal medullary sarcoma (neuroblastoma) in children for the orbits and skull [7] and the generalized infiltrating metastatic osteogenic carcinomatosis of the skeleton occasionally resulting from a primary carcinoma of the prostate gland [8] Such examples might be compared with the secondary pyaemic foci limited to the bony skeleton which formerly occasionally occurred in septic cases

In regard to the way in which in our case the maternal melanotic tumour inoculated the foetal circulation by growing through the placenta an analogy may be found in what happens in cases of *true* congenital tuberculosis but of course tubercle bacilli are much less likely to be held up in the blood capillaries of the foetal liver than are large tumour cells Some years after Koch s discovery of the tubercle bacillus it was maintained that the bacillus could not pass through the placenta and infect the foetus *in utero* and it was held that only a constitutional predisposition towards tuberculosis could be inherited and even that was denied by many authorities However it was soon proved that in very rare cases the foetus was actually infected *in utero* owing to the tuberculous process in the mother infecting the placenta and producing one or more tuberculous lesions in the placenta By means of such placental lesions the tubercle bacilli were enabled to grow through the placenta with a resulting tuberculous inoculation of the foetal circulation and true congenital tuberculosis It was alternatively but less convincingly suggested by A Sitzenfrey in 1909 [9] that tuberculous foci localized in the decidua vera might penetrate the amnion infect the liquor amnii and thus give rise to intrauterine infection of the foetus—indeed F W Andrewes [10] already in 1903 had suggested that pre natal tuberculosis might in some cases possibly be caused by the foetus swallowing liquor amnii containing tubercle bacilli derived from a disintegrating lesion of the placenta How rare cases of true congenital tuberculosis must be may be judged by the fact that in 1916 one of us (F P W) was able to summarize all the hitherto proved and probable cases of true congenital tuberculosis in an article published in the *British Journal of Children s Diseases* [11]

of the abdomen and thorax The uterus was above the usual size at term and a large soft mass occupied the lower segment On April 9 I delivered a live child by Caesarean section The lower uterine segment was occupied by a huge black placenta which proved to be infiltrated with masses of melanotic growth The mother made a smooth recovery and the child left the hospital thriving and without evidence of disease

There are many remarkable published examples and different varieties of inherited constitutional predisposition to malignant neoplasms [2] Especially notorious is the constitutional predisposition to familial multiple polyposis of the large intestine [3] We would suggest that J S Manson s examples of the hereditary transmission of sarcoma (mother and two sons affected with lymphosarcoma) [4] were examples of inherited constitutional predisposition to lymphosarcoma and analogous to rare cases of familial tendency *to lymphatic leukaemia [5] which like myeloid leukaemia* is probably also of neoplastic origin Our present case as above stated has nothing to do as far as we can judge with any inherited constitutional predisposition to malignant neoplastic growth

It is as mentioned above apparently the first case of the kind reported in human pathology We have not even heard of any *analogous case in animals – that is to say a case of congenital* malignant tumour due to intrauterine inoculation of the foetus by the passage of malignant tumour cells from the placenta to the child by way of the umbilical vein Nature s experiment in the present case could only be imitated in experimental animal pathology by inoculating the blood stream of the umbilical vein at the moment of birth with a dilute emulsion of tumour cells obtained from a sarcoma or carcinoma that had previously developed spontaneously or had been artificially produced in any part of the mother s body

Professor J A Murray has however kindly referred us to a paper by Dr Makoto Takahashi [6] who also quotes similar experimental work carried out by other investigators on rats or mice Takahashi produced growths in the lungs by the intravenous injection of *carcinomatous or sarcomatous material* He found that a large proportion of the cells introduced into the blood stream disappeared after undergoing vacuolation surrounded by leucocytes Although the lung capillaries formed an efficient filter some tumour cells were able to pass through the lungs and give rise to growths in various parts of the body The cells which passed through the lungs and

XXXIII

CYSTIC LYMPHO EPITHELIOMA OF THE THYMUS—NERVOUS AND OTHER CLINICAL SYMPTOMS IN THE ADULT[1]

F PARKES WEBER and K BLUM

In this paper we are concerned not with the simple tumours—fibroma lipoma lymphangioma lympho-sarcoma round-cell sarcoma—which occasionally (though rarely) arise in the thymus as in other parts of the body but with those which arise from the essential epithelioid cells of the thymic medulla associated in greater or lesser proportion with lymphocyte like cells (probably really lymphocytes) such as constitute the normal thymic cortex These primary thymic tumours—true thymomata—may be termed lympho-epitheliomata (Grandhomme 1900 Schmincke 1921 Regaud 1921) and are much less often malignant than are the primary lympho epitheliomata of the tonsils pharynx and nasopharynx (Cappell 1934 Harvey Dawson and Innes 1937) *For recent histological accounts of thymic lympho-epitheliomata see* Wu (1935) and Obiditsch (1937)

The thymic lympho-epitheliomata seem in some cases to exert an endocrine effect and are specially related to myasthenia gravis Most important and interesting was the original observation by Weigert (1901) of a thymus tumour in a case of myasthenia gravis in which he wrongly interpreted the lymphorrhages in the muscles as tumour metastases To these questions we will return in the discussion further on but for a summary of the literature of the subject we must refer to the recent papers by Gold (1935) Meister (1936) Norris (1936) Miller (1940) Blalock *et al* (1941) and Poer (1942)

Case Record

The patient Mrs F F aged 58 years was admitted on November 5 1941 with irregular pyrexia of uncertain origin The history was that after a sore throat six weeks ago she had been suffering from pains in various parts Blood count Haemoglobin 60 per cent erythrocytes 3 610 000 colour index 0 8 leucocytes 9 000 (polymorphs 53 per cent lymphocytes 40 per cent monocytes 7 per cent) Blood sedimentation first hour 70 two hours 120 Blood-culture negative Urine nothing abnormal By auscultation a blowing systolic murmur could be heard in the left intercostal space

[1]After the *Journal of Neurology and Psychiatry* 1942 5 149

In our present paper it would perhaps have been better to use the term malignant melanoma instead of melanotic sarcoma as it might possibly be suggested that the primary growth in the mother (the site of which is not certain) was a melanotic carcinoma The tumours in the child's liver were obviously of multiple metastatic type and it is the absence of any primary tumour in the child that makes the case unique the real primary growth having been of course in the dead mother The inoculation of the child may have taken place not long before or even at birth Whether any exactly analogous case has been observed in animals we do not know

The liver now in the museum of the Royal College of Surgeons of England was demonstrated by us on February 28 1930 at the Section for the Study of Disease in Children of the Royal Society of Medicine

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had a honeycomb appearance on section most of the cysts freely communicated with each other and were filled with a slimy translucent mucoid fluid their walls had a smooth inner surface In the upper portion of the tumour was a slightly larger cavity which was filled with what macroscopically appeared to be pus but no microbes could be detected in a film stained with methylene blue or by Gram s method

Thyroid gland slightly enlarged showing nodular adenomatous condition one of the nodules in the left lobe having a calcified capsule Broncho-pneumonia of the lower lobe of the right lung purulent bronchitis Nothing specially noteworthy in the other organs brain heart liver spleen pancreas adrenals kidneys uterus ovaries gastro intestinal tract larynx

Microscopical Examination

The solid part of the mass consisted of a dense collagenous fibrous framework in which were embedded cellular islands consisting of delicate spindle and epithelioid cells with vesicular nuclei associated with lymphocyte like cells as in so-called thymic lympho epitheliomata No Hassal s corpuscles were seen but at one spot several elongated slightly curved (banana shaped') vesicular nuclei were noted grouped together so as to suggest a faint attempt at the formation of a Hassal s corpuscle In their shape some of the so-called spindle cells resemble rather the cells of oat-cell bronchial carcinoma Microscopical examination of what macroscopically had appeared to be pus showed that it consisted of this cellular material breaking down (softened) as a result of (ischaemic?) necrosis It may be mentioned that a film of this pseudo-pus stained with methylene blue showed the presence of a considerable number of tissue mast cells which were not clearly differentiated in sections stained in other ways The honeycomb cystic portion of the tumour represented apparently a further stage of aseptic necrotic involution of the lympho-epitheliomatous tissue The process was probably analogous to the occasional changes in the thymus gland of children leading to the formation of Dubois s abscesses or pseudo-abscesses formerly supposed to be necessarily connected with congenital syphilis

Is the mass to be regarded as a real lympho-epitheliomatous tumour of an ectopic thymus (or thymic rest') with secondary cystic degenerative changes as above explained or is it an example of hypertrophy of an ectopic thymus (or thymic rest') containing cysts resulting from involutionary focal ischaemic necrotic processes (Kopac

close to the sternal margin X ray examination of the heart (Dr F G Wood) showed a rounded mass projecting to the left of and apparently continuous with the heart shadow and moving with it right and left oblique views were thought to point to this projection being an enlargement of the pulmonary artery and conus Brachial blood pressure 135/80 mm Hg Blood Wassermann reaction negative Ophthalmoscopic examinations (Dr C Markus) showed hyperaemia especially left eye apparently connected with hypermetropia The patient at various times complained of a severe kind of acroparaesthesia and of numbness (no real anaesthesia) of the right lower limb and afterwards of the right upper limb and both lower limbs Severe cramps were sometimes complained of The knee jerks which were equal and natural on admission were unequal at the end of November the left one being greatly exaggerated In March 1942 the patellar and Achilles reflexes were absent on both sides the triceps reflex was absent on the right side present on the left side the plantar reflex was of the normal flexor type on both sides no superficial abdominal reflexes were obtained Both pupils reacted normally The speech was rather sluggish Very little tactile responses in either lower limb some hypersensitiveness to pressure over the sciatic nerve both sides The patient tended to keep her knee joints flexed Although general asthenia was very marked no definite characteristic features of myasthenia gravis were noted

Focal infection was thought of but no focus could be discovered There was moderate fever from admission to November 25—then a little at the commencement of December and from December 10 to the commencement of January 1942 About February 5 there was again fever and then from February 22 to the patient s death on March 17 1942 which was due to a final broncho-pneumonia with some decubitus Frequent profuse night sweatings constituted also a clinical feature The last blood culture yielded a growth of *Staphylococcus albus* Amongst the drugs tried sulphapyridine on one or two occasions seemed to exert temporary beneficial effect

Necropsy

Over the front upper part of the heart and slightly to the left firmly connected with the fibrous layers of the parietal pericardium was a bun shaped mass about the size of half a large orange 14 × 8 × 6 cm in measurement (weight after preparation as a museum specimen 112 grammes) The multilocular cystic central portion of the mass

analogy with what happens in some cases of lympho granulomatosis maligna be attributed to the necrotic softening and formation of pseudo-pus in the lympho epithelioma with resulting toxic absorption Patients with thymic lympho-epithelioma according to the literature (Matras and Priesel 1928 Zajewloschin 1929 and 1933 Nemenow 1932 Ercklentz 1936) have died of pleuritis empyema pneumonia furunculosis and decubitus The loss of resistance to toxic infectious agents culminated in our case with the decubitus and broncho pneumonia the latter first manifest four days before the patient s death the former a week earlier It is possible that the absence of definite symptoms of myasthenia gravis might be due to the diminution of the (presumably active) function of the epithelioid cells consequent on the necrotic softening of many of the latter associated with the formation of the pseudo pus and cysts

In regard to clinical diagnosis the X ray shadow of a thymic



FIG 1—Radiogram of the thorax taken on November 20 1941

1939)? The spindle and epithelioid cells resemble those of normal thymic medulla and the lymphocyte like cells resemble those of normal thymic cortex—which most authors now regard as true lymphocytes—but the grouping of these two constituent types of cells is not sufficiently clearly marked out into cortex and medulla to permit the mass to be regarded as the result of mere thymic hypertrophy nor does the complete absence of Hassal s corpuscles favour the view of mere hypertrophy The mass must therefore we think be regarded as a true primary thymic lympho-epitheliomatous tumour ('thymoma') Whether the tumour is a primary one of an ectopic thymus or of a thymic rest makes no difference from the pathological point of view we did not specially search for any thymic remnant in the normal position By our term ectopic we do not imply that the position of the tumour in front of the pericardium is abnormal for thymic tissue in early childhood In the present case there were no metastases and nothing in the microscopical examination pointed to malignancy

Discussion

Clinical symptoms from thymic hypertrophy or tumour may of course be mechanical from local pressure and in the present case the systolic murmur heard to the left of the sternum was probably due to tumour pressure

If the thymus is an endocrine organ one would expect that constitutional endocrine symptoms would often result—as they often do in primary tumours of other endocrine organs—from a primary neoplasm arising from the essential (endocrine) cells that is to say so long as the neoplastic cells still retain something of the original functional (endocrine) activity in fact so long as the neoplastic cells functionally still resemble the cells of simple hyperplasia

In something like 55 per cent of cases of myasthenia gravis hypertrophy or primary tumour (lympho-epithelioma) of the thymus has been present but in reality the percentage is probably considerably higher for in many cases thymus or thymic tumour has not been sufficiently looked for On the other hand myasthenic symptoms may have been overlooked in some cases of thymic tumour in surgical wards (Mann 1934) Although in our present case characteristic symptoms of myasthenia gravis were absent it is possible that the great general asthenia the extreme acroparaesthesia numbness and other nervous symptoms were in some way connected with thymic tumour The recurrent sweating and pyrexial periods may possibly by

from myasthenia gravis and Graves' disease, who temporarily completely lost her myasthenic ophthalmoplegic symptoms under the influence of prostigmin. Dudgeon and Urquhart (1926) in nine cases of Graves' disease found muscle 'lymphorrhages' similar to those of myasthenia gravis.

It seems that in very rare cases malignant thymoma or primary carcinoma of the thymus may by some unknown process disturb the endocrine balance in such a way as to give rise to symptoms somewhat resembling Cushing's syndrome (Leyton, Turnbull and Bratton 1931) but into this question of the Leyton-Turnbull-Bratton syndrome we cannot enter here.

For help in the microscopical examination we have specially to thank Dr. J. R. Gilmour, Dr. R. W. Scarff, Dr. H. M. Turnbull, Dr. J. G. Greenfield and Dr. A. H. T. Robb-Smith. We owe the photomicrograph to Dr. Greenfield. The tumour itself is now in the Museum of the Royal College of Surgeons.

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tumour is of *great importance* *In our case it seemed to move with* the pulsation of the great vessels and to be continuous with the heart shadow The position of the tumour in the anterior mediastinum overlapping the parietal pericardium on the left was not made out during life In the differential diagnosis during life cardiac aneurysm pericardial tumour mediastinal lympho-granuloma mediastinal gumma mediastinal phlegmon and congenital dilatation

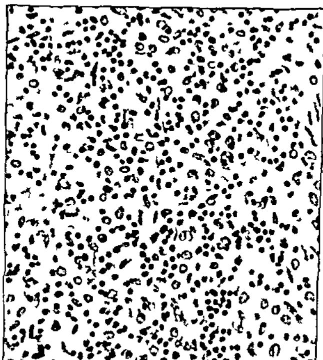


Fig 2 —Photomicrograph of part of the tumour showing the characteristic epithelioid and lymphocyte like cells (×400)

of the pulmonary artery might be thought of Had the correct diagnosis been made at an early stage our case would have been an ideal one if not for surgical excision of the tumour at least for treatment by X rays or radium—that is to say if one believes that the thymic tumour played any part in the patient s severe illness

The possible part played by the thymus gland in some cases of Graves disease is suggested by the occasional occurrence of myasthenic symptoms in the latter disease and even by satisfactory results of thymectomy (Schumacher and Roth 1913 Russell Brain 1938 Adler 1939) Fraser (1937) recorded the case of a woman suffering

XXXV

CARCINOMA TELANGIECTATICUM[1]

F PARKES WEBER

Telangiectatic carcinoma deserves a special niche in clinical medicine just as cancer en cuirasse and Paget s disease (of the nipple etc) do although it cannot be shown that the cancer cells themselves in cases of telangiectatic carcinoma differ from those in other cases of mammary carcinoma Why the cancer cells in cases of telangiectatic carcinoma should spread specially in the super ficial blood capillaries of the cutis instead of through the lymphatics and connective tissue spaces as in cancer en cuirasse remains more or less a mystery

Hermann Küttner of Breslau in 1924 differentiated what he called erysipelas carcinomatosum [1] clinically and histologically from cancer en cuirasse and showed that the former spread locally by the (superficial) blood vessels whilst the latter extended through the lymphatics and connective tissue spaces around it so as to produce very marked scleroderma like hardening of the skin

C Rasch of Copenhagen prefers the term carcinoma erysipe latodes – that is to say he would speak of carcinoma resembling erysipelas rather than carcinomatous erysipelas – because the cases are not cases of true erysipelas at all In his paper of 1931 [2] Rasch points out that a characteristic of this erysipelatoid carcinoma is that it grows subepidermally in the underlying blood vessels without attacking the epidermis whilst Paget s disease grows within the epidermis

In a communication under the heading *Carcinoma Telangiecta ticum* on July 8 1933 at the annual meeting of the British Associa tion of Dermatology [3] I chose the term telangiectatic carcinoma in preference to erysipelatoid carcinoma because my case at least was neither in appearance nor in its other clinical features at all like erysipelas Dr N C Van Vonno (of Breda) who was present at the meeting told me of a similar case under his care in Holland and shortly described it as Carcinoma Telangiectaticum after my paper in the *British Journal of Dermatology and Syphilis* [4]

My patient Mrs E T aged 48 years was a married Englishwoman of medium size and general nutrition The following is from my account in *July 1933* In October 1932 her left mamma was ampu

[1]Reprinted with permission from *International Clinics* (1935) series 45 3 145 148

XXXIV

A NOTE ON HAEMATOSPERMIA[1]

F PARKES WEBER

My interest in the subject was originally due to my writing an abstract of a paper on haematospermia for a medical journal about 1893 Although a possible analogy with the discharge of sanguineous matter through the female nipple owing to a mammary tumour may suggest itself there seems to be no justification for much alarm in most cases The blood seems generally to be derived from the prostate or prostatic mucosa and in one patient whom I knew a drop or two appeared at the urethral orifice in connexion with defaecation as it expressed from the prostate by the passage of hard faeces This phenomenon lasted only for some weeks or months but in the case in question the haematospermia lasted on and off for twenty o thirty years – in fact till seminal emissions practically ceased after the age of 70 years or thereabouts The exact cause of this benign type of haematospermia is not likely to be proved as it does not appear to disturb the general health or shorten life whatever the exact cause may be At a post mortem examination in old age the previous occurrence of frequent haematospermia is likely not to reach the ears of the examining pathologist unless the patient were to mention in his will that he wished thirty guineas paid for specially investigating the subject but in really old age the patient himself may have forgotten all about it

[1]From a letter to the *British Medical Journal* 1940 2 729

also involved a large area of skin over the right mamma and part of the right front of the chest On the left side the operation scars were especially affected In some parts the process was spreading by the formation of small telangiectatic islets The telangiectatic margins and islets were somewhat raised above the general level of the skin

In the telangiectatic areas individual dilated blood vessels were very conspicuous in association with diffuse redness due to telangiectasis of the minute blood capillaries By pressure under glass



Fig 2—Photomicrograph of a section from the margin of the telangiectatic region on the right side of the thorax (June 1933) For this I am indebted to Prof J C G Ledingham See description in the text

the blood could not be squeezed out of some of the dilated blood vessels but there were no blood extravasations (no purpuric elements) present The reason why the blood could not be squeezed out of some of the telangiectases was doubtless that minute blood vessels had their lumen blocked by cancer cells In part the skin showed a little brown pigmentation and in other parts a slightly glossy change Very little itching or paresthesia of any kind was associated with the trouble according to the patient

There was no enlargement of axillary or other lymphatic glands to be made out The blood serum gave negative Wassermann and Meinicke reactions Brachial blood pressure systolic 155 diastolic 80 mm Hg The blood count showed slight anaemia Otherwise there was nothing abnormal by ordinary examination of the patient

tated for carcinoma and the axilla was cleared out At the time of operation there was a curious telangiectatic condition of the skin over the mamma and a small area of skin in the left axilla had a similar appearance Almost all of the telangiectatic skin was removed together with the carcinomatous mamma Since the operation the telangiectatic process which in most parts showed a very definite spreading margin had extended so as to involve a great portion of the skin on the front and back of the left half of the thorax and had

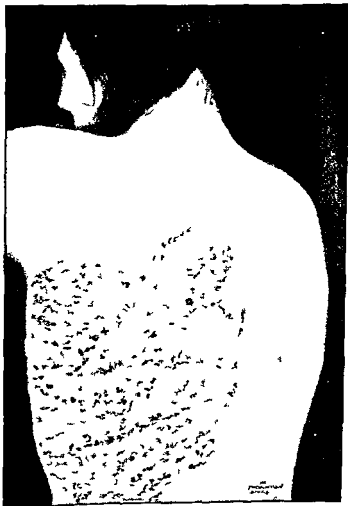


Fig 1 —Carcinoma telangiectaticum Appearance of the left back of the thorax in June 1933

telangiectaticum is preferable to *erysipelas carcinomatosum* (Kuttner) or *carcinoma erysipelatodes* (Rasch) I have little doubt that the telangiectatic cancerous condition in these cases spreads mainly if not entirely in the lumen of the blood capillaries of the skin though the lymphatics and connective tissue spaces may likewise in some parts be involved H W Barber s case [5] shown at the Royal Society of Medicine London on December 17 1931 seems to have been a mixture of the condition seen in my patient with cancer en cuirasse and Paget s disease and I expect that the association of two or all three of these carcinomatous processes in the skin will be occasionally observed

I am indebted to Dr W E Barnard Mrs G Hilton Professor J C G Ledingham and Dr J W McNee for help in the investigation and treatment of this patient

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Menstruation was still regular She had never been treated with Roentgen rays for the mammary carcinoma or for anything else

Microscopical examination – A piece of skin from the margin of the telangiectatic region on the right side of the thorax was excised by Mr H Rast on June 19 1933 Microscopical sections showed enormous dilatation of the cutaneous blood capillaries which contained clumps of cancer cells and here and there a little blood Activity in the cancer cells was evidenced by the presence of several mitotic figures but the central portions of some of the clumps were necrotic It was possible that some of the vessels containing cancer cells but in which no blood was seen were lymph capillaries There was very little evidence of inflammatory reaction Microscopical examination of little red telangiectatic nodules on and about the scar on the left front of the thorax proved that they also were carcinomatous

Subsequent history of the case – In the latter part of July 1933 the patient was admitted to University College Hospital London for careful superficial roentgen ray therapy (a small area of skin at a time) This treatment was subsequently continued in the out patient department The effect of the roentgen ray therapy was to remove much of the superficial redness but the condition gradually spread so as to involve almost the whole skin of the thorax (and of the front of the abdomen downwards nearly to the umbilical level) before the patient died in the German Hospital on May 13 1934 The right mamma the left pleura and the lymphatic glands in both axillae and the left supraclavicular fossa had been involved since November 1933 or earlier The right pleura had been involved since March 1934 There had been no marked cachexia in the patient s general appearance before March 1934

The post mortem examination showed complete cancerous adhesion of the pleura on both sides the adherent pleura was harder and thicker over the left lung than over the right There was an infiltrated superficial lymph gland below the sternal end of the left clavicle which had developed under observation in the hospital The pericardium was not obviously involved but there was some cancerous change of the peritoneal surface of both the right and left halves of the diaphragm No distant cancerous metastases were noted Microscopical sections of the right mamma and of the thickened adherent pleura showed carcinoma the characters of which suggested that the original (primary) carcinoma in the left mamma was a duct carcinoma

In conclusion I would again suggest that the term *carcinoma*

mental abnormality it is not surprising that it should be occasionally associated with congenital malformations [2] such as spina bifida [3] and cerebral meningocele [4] (figs 1 and 2 represent a neurofibromatous woman with what I wrongly took to be a suprazygomatous





FIGS 1 and 2—Case of cutaneous neurofibromatosis The patient has a left lateral (suprazygomatic) soft fibromatous fold of skin or pachydermatocele such as are occasionally met with in Recklinghausen's disease there is a tuft of hair below it I at first mistook this for a meningocele (F Parkes Weber *Proc Roy Soc Med* (Clin Sect) Lond 1925 18 1) Compare also Weber F Parkes and Bode O B 1934 *Proc Roy Soc Med* 27 638

XXXVI

PERIOSTEAL NEUROFIBROMATOSIS, WITH A SHORT CONSIDERATION OF THE WHOLE SUBJECT OF NEUROFIBROMATOSIS[1]

F PARKES WEBER

WITH THE COLLABORATION OF J R PERDRAU

NEUROFIBROMATOSIS is often called Recklinghausen s disease from von Recklinghausen s description of multiple cutaneous fibromata in 1882 [1] but this is rather confusing since the diffuse and generalized forms of osteitis fibrosa or fibrocystic disease of bones now known to be due to hyperparathyroidism are also spoken of as Recklinghausen s disease and in certain cases of neurofibromatosis there are bony thickenings which when they are localized on the face or skull may clinically be supposed to be due to a kind of osteitis fibrosa one cause of the clinical appearances known as leontiasis ossea I believe however that the irregular cranial hyperostoses in cases of neurofibromatosis are probably due not to the changes of osteitis fibrosa but to neurofibromatous involvement of the periosteum just as the irregular thickening of the shaft of the left tibia in the case we shall describe was due to the irregular localized neurofibromatosis of the periosteum Hyperplasia of the bone underlying or close to a plexiform neuroma or a neurofibromatous pachydermatocele (neurofibromatous elephantiasis and molluscous pendulous tumours one form of so called dermatolysis) has long been recognized as of occasional occurrence and this doubtless applies to some of the cases of bony hyperplasia in the face and head in cases of neurofibromatosis

Neurofibromatosis is evidently of congenital and developmental origin and is not rarely familial In regard to the post natal development of most of its worst manifestations it resembles many other developmental diseases that may be familial such as generalized telangiectasia of the skin and mucous membranes (hereditary epistaxis etc) multiple exostoses the delayed examples of hereditary oedema of limbs (the Nonne Milroy disease trophoedema Meige s disease) progressive lenticular degeneration with hepatic cirrhosis (Wilson s disease) familial developmental ataxia myotonia atrophica various primary muscular dystrophies and hereditary cataract

As neurofibromatosis is the manifestation of a congenital develop

[1]Enlarged from the *Quarterly Journal of Medicine* (1930) 23 151 (Dr Perdrau died in 1939)

of the face must be exceedingly rare Dr Perdrau once examined the kidneys from an undoubted case of tuberous sclerosis of the brain and they contained true neurofibromata [6] The following are the chief component signs of the disease most of which are directly due to the neurofibromatous process

The Cutaneous Pigmentation

This is often the earliest sign of the disease and is present in nearly all cases It usually takes the form of greyish brown *cafe au lait* spots and patches of various shades sizes and numbers distributed especially over the trunk To these may be added much darker spots and occasionally there may be symmetrical sheet like pigmentation not very dark of large areas as the face (facies faunica') or neck and shoulders The pigmentary formes frustes of Recklinghausen s disease are in reality mostly early stages developing later into the fully developed disease Thus a girl aged 14 years whom I described in 1905 as a case of Unusual Cutaneous Pigmentation possibly allied to Recklinghausen s Disease in addition to scattered *cafe-au lait* and darker spots had diffuse sheet like pigmentation of the upper part of the back and neck (*see* fig 3) well seen in the drawing by Miss Mabel Green reproduced with a later account published in 1909 When she was examined again in 1926 after she had been married for





FIG 4 *a* and *b*—Recklinghausen s disease The same case in 1926 when fully developed with numerous molluscous fibromata

meningocele) Perhaps this *developmental connexion is aetiologically* closer with unilateral buphthalmus (congenital glaucoma) and haemangiectatic and so-called anaemic naevi [5] A typical case of neurofibromatosis with congenital absence of the right ulna was shown by Haldin Davis at the Royal Society of Medicine November 19 1931 (not reported in the *Proceedings*) Hereditary combination with epidermolysis bullosa has been recorded [5]

The disease consists chiefly in the formation of fibromatous neoplasms arising from the connective tissue elements of the nerves including it has been claimed the sheath of Schwann and perhaps the rarity of growths in the central nervous system itself is due to the absence of this sheath in the medullated fibres of the white substance According to some authors neurofibromatosis may be occasionally associated with sclerotic or gliomatous patches in the central nervous system but its association with tuberous sclerosis and with Pringle's telangiectatic type of so-called sebaceous *adenomata*

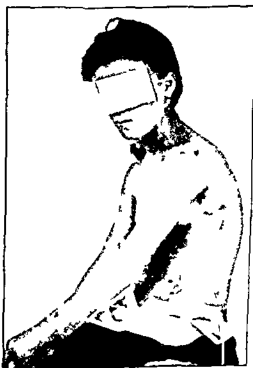


Fig 3—Recklinghausen's disease A girl with a pigmentary forme fruste when seen in 1905 at the age of 14 years This photograph was not illustrated in my published account of the case

of the face must be exceedingly rare. Dr Perdrau once examined the kidneys from an undoubted case of tuberous sclerosis of the brain and they contained true neurofibromata [6]. The following are the chief component signs of the disease most of which are directly due to the neurofibromatous process.

The Cutaneous Pigmentation

This is often the earliest sign of the disease and is present in nearly all cases. It usually takes the form of greyish brown *cafe-au lait* spots and patches of various shades sizes and numbers distributed especially over the trunk. To these may be added much darker spots and occasionally there may be symmetrical sheet like pigmentation not very dark of large areas as the face (facies faunica) or neck and shoulders. The pigmentary formes frustes of Recklinghausen's disease are in reality mostly early stages developing later into the fully developed disease. Thus a girl aged 14 years whom I described in 1905 as a case of Unusual Cutaneous Pigmentation possibly allied to Recklinghausen's Disease in addition to scattered *cafe au lait* and darker spots had diffuse sheet like pigmentation of the upper part of the back and neck (*see* fig 3) well seen in the drawing by Miss Mabel Green reproduced with a later account published in 1909. When she was examined again in 1926 after she had been married for



FIG 4 *a* and *b* —Recklinghausen's disease. The same case in 1926 when fully developed with numerous molluscous fibromata

some years and had a child she was a characteristic example of Recklinghausen s disease (fig 4) with the usual pigmentation and molluscous fibromata and a diffuse soft cushion like mass in the subcutaneous tissue of the outer part of the right thigh and a slightly tender swelling on the right side of the lower part of the neck probably connected with a nerve trunk [7]

Soldan [8] concluded that the cutaneous pigment spots in Recklinghausen s disease were probably a direct result of the neurofibromatous *process in the cutaneous nerves but this is very doubtful* The congenital examples seem to be indistinguishable from ordinary simple pigment naevi

The Cutaneous Fibromata

The molluscous fibromata are so well known that they need no elaborate description and indeed they used to be known long ago as multiple molluscous tumours of the skin They are situated chiefly on the trunk and in number they vary from a few to many hundreds and in size from miliary to larger than an orange In the illustration (fig 5) from the photograph of a woman (Mrs M K) aged 40 years



Fig 5—Recklinghausen s disease A woman (Mrs M K) aged 40 years with some fairly large molluscous fibromata on the *left* upper arm The photograph was taken in January 1904 and several years later (December 10 1909) I showed the patient at the Clinical Section of the Royal Society of Medicine (*Proc Roy Soc Med* (Clinical Section) 1909 1910 3 79) but my account was accompanied by a different illustration showing the appearance of the patient s back The molluscous fibromata were said to have gradually appeared after typhoid fever at the age of 18 years There was typical though *relatively slight* cutaneous pigmentation

some fairly large molluscous fibromata are seen on the left upper arm They may be scarcely raised or much raised sessile or pedunculated Those with a thin pedicle are said occasionally to drop off spontaneously They are formed from the connective tissue elements of the small cutaneous nerves as the tumours of the deeper nerve trunks are from the endoneurium perineurium or epineurium or sheath of Schwann It is not to be wondered at that nerve fibres may be occasionally included or carried into all kinds of neurofibromata and in those of young patients it seems that newly formed nerve fibres have occasionally been found In two or three cases with multiple scattered peripheral tumours clinically resembling Recklinghausen s disease microscopic examination of the tumours has shown them to be ganglioneuromata (Lhermitte and Dumas) In consistence the cutaneous neurofibromata are mostly soft as the adjective molluscous (*mollis*=soft) implies but vary considerably some of them undergo a myxomatous change and become so soft and atrophic that they resemble a shrivelled grape in appearance sometimes even on palpation they seem to form cavities in the skin imperfectly filled with fluid into which the finger tip can easily be pressed so that they are reminiscent of some of the spots met with in cases of macular atrophy of the skin Whether the so called multiple benign *cutaneous tumours of Schweniger and Buzzi are atrophic forms* of molluscous fibromata is doubtful

Just as one or two congenital simple pigment naevi exactly resembling the ordinary pigment spots and patches of Recklinghausen s *disease are* so frequently met with in ordinary healthy persons as hardly to constitute an abnormality so I believe that the presence of one or two small molluscous fibromata is not at all rare in otherwise normal persons

There is no doubt that sudden aggravation of the manifestations of Recklinghausen s disease may be due to metabolic or endocrine factors especially pregnancy so that indeed it sometimes seems as if the onset of molluscous fibromata were due merely to pregnancy They were said to have gradually appeared after typhoid fever at the age of 18 years in the case of a woman already referred to (fig 5) Some that have appeared during pregnancy have disappeared after pregnancy [9] as certain rare haemangiectatic manifestations occasionally do Some also may atrophy or practically disappear independently of pregnancy Though the manifestations of neurofibromatosis are largely influenced by endocrine factors it seems to me that it would be quite wrong to conclude as some have apparently

done that neurofibromatosis is a disease of endocrine origin Various endocrine *symptoms have it is true been observed in patients with* undoubted neurofibromatosis symptoms of Addison s disease in a few cases symptoms of acromegaly or incomplete Frohlich s syndrome of precocious or *retarded sexual development or dwarfism* and of thyroidal disturbance – but even so it must be remembered that the sella turcica or pituitary gland might be directly affected by the neurofibromatous process just as neurofibromatous filaments have been found though rarely in the suprarenal gland when symptoms of Addisonism had been noted [10] Unilateral supposed mammary hypertrophy in children with neurofibromatosis may well be due to a molluscous kind of dermatocele or local molluscous elephantiasis allied to plexiform neuroma (neurofibroma)

Neurofibromatosis of Nerve trunks

This is a graver and sometimes a later manifestation of the disease In the most typical cases one or more sometimes several of the nerve trunks can be felt to be affected especially by palpitation of the extremities and sides of the neck Along the course of the affected nerves there are one or more often several bead like nodules which may distend the nerve affect one side of it or be loosely attached to its sheath in the neck such movable nodules may be mistaken for enlarged lymphatic glands or the whole nerve may be uniformly or irregularly thickened by an interstitial neurofibromatosis for a variable length *It might even be suspected that the diagnosis* of familial chronic hypertrophic interstitial neuritis had been made in such cases but the thickening is likely to be much greater than in the hypertrophic neuritis cases which are probably still rarer The diffuse or beaded neurofibromatous thickening of nerve trunks in the extremities is rarely visible on mere inspection well illustrated in the great monographs of R W Smith (1849) and Alexis Thomson (1900) More centrally situated tumours on the roots of the spinal and cranial nerves and on the cauda equina are a feature of some cases Neurofibromata of the acoustic nerve and others in the ponto-*cerebellar groove in the absence of generalized neurofibromatosis* like isolated neurofibromata elsewhere constitute a somewhat special class The more centrally situated neurofibromata of the nerve trunks are doubtless more likely to undergo malignant sarcomatous change than the cutaneous neurofibromata but they may also mechanically injure the central nervous system and even penetrate into it

With these cases of intracranial neurofibromata Wishart s syndrome should be compared – *see J H Wishart Tumours in the Skull Dura Mater and*

Brain *Edinb Med and Surg Journ* 1872 18 393 and the elaborate paper in *Brain* 1937 60 85 by C Worster Drought W E Carnegie Dickson and W H McMenemey entitled Multiple Meningeal and Perineural Tumours with Analogous Changes in the Glia and Ependyma (Neurofibroblastomatosis) —with abundant references to the literature of the subject Cf L Minski Familial Bilateral Acoustic Tumours *Journ Neurol and Psychopath* 1932 12 289

Plexiform Neuroma 'Elephantiasis Nervorum', Pachydermatocele etc

The condition known as plexiform neuroma (or neurofibroma) is an exaggeration of the more diffuse neurofibromatosis of nerve trunks mentioned above It is mostly subcutaneous It may occur in one half of the tongue and constitute the condition which Shattock termed hemimacroglossia neurofibromatosa [11] When it is sub cutaneous the thickened nerve cords are sometimes felt surrounded by much loose fibrous tissue [12] Sometimes the loose fibrous tissue forms the chief part of a subcutaneous and cutaneous swelling in which enlarged neurofibromatous nerves can be felt Thus the con dition is allied to the diffuse swelling known as pachydermatocele or chalastodermatocele and pachydermatoceles the flounce like or fold like tumours (Lappen Elephantiasis) and pendulous tumours of the same nature merge into the condition of neurofibromatous elephantiasis In fact all these conditions have been sometimes loosely spoken of as localized forms of elephantiasis —that is to say elephantiasi nervorum Probably the periosteum in the neighbour hood of such diffuse elephantiastic swellings [13] is often also neuro fibromatous and thickened and then the bone under the periosteum is likely to be hyperplastic Anyhow there are many accounts of cases of irregular cranial hyperostosis associated with plexiform neuroma or the allied condition of pachydermatocele [14]

Neurofibromatosis of the Mucous Membranes Viscera and Sympathetic and Parasympathetic Nerves [15]

It will be sufficient here to mention that in rare cases neurofibromata have been found in the mucous membranes as in the skin In rare cases neurofibromata have been detected in the stomach (16) urinary bladder (16) and various viscera there were several small neurofibro mata on the peritoneal surface of the ileum in the case we shall describe farther on There are neurofibromatous polyps of the anus or rectum It seems that visceral neurofibromata are especially liable to undergo a sarcomatous change

The vagus and sympathetic nerves [16] may be affected including probably the periarterial nerve plexuses supplying the limbs a

possible explanation of circulatory disturbances in the extremities met with in very rare cases of neurofibromatosis Involvement of the cervical sympathetic may give rise to Horner s syndrome There is scattered literature on intrathoracic neurogenic tumours

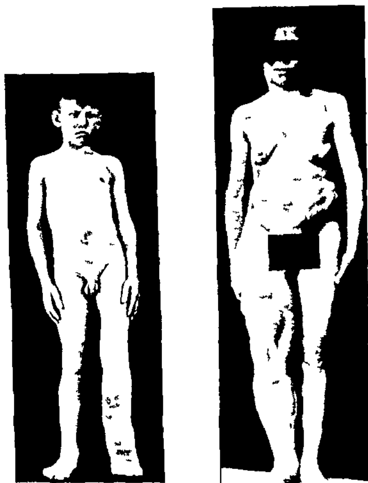
The Osseous and Periosteal Manifestations of Neurofibromatosis

I need not again allude to the many various bony congenital abnormalities and malformations which have been occasionally met with in connexion with neurofibromatosis nor need I mention the changes due to acromegaly in the very rare cases in which acromegaly has been *associated with Recklinghausen s disease*

In a considerable proportion of the subjects of Recklinghausen s disease there has been scoliosis or kyphosis or kypho-scoliosis Pelvic deformity due to bone softening has also been observed Gould [17] from a rather limited anatomical and histological examination of such cases came to the conclusion that the bone softening was microscopically and macroscopically indistinguishable from that of osteomalacia But if this conclusion is correct it does not necessarily follow that some affection of the endocrine glands is the primary cause of the phenomena of Recklinghausen s disease It must not be forgotten that spinal curvature is relatively quite as frequent probably more frequent in cases of syringomyelia where local bone softening is probably also the cause and yet no one suggests that the *primary cause of syringomyelia is to be found in the endocrine* glands Moreover neurofibromata of the roots of spinal nerves might in some cases be conceivably a cause of the spinal curvature – there might even be a congenital vertebral malformation or there might be though I think this unlikely a local periosteal neurofibromatosis of vertebrae as suggested by Brooks and Lehman [18] Their work constitutes a most important advance in the understanding of the bony changes met with in neurofibromatosis

These authors made a careful examination in seven cases of Recklinghausen s disease with bone changes In their Case 2 a boy aged 12 years *(fig 6) there was a condition of neurofibromatous* elephantiasis of the left leg and the left tibia was longer than the right one In their Case 6 a boy aged 9 years the left thigh was longer than the right one and showed an area of neurofibromatous elephantiasis In Lehman s Case 8 a woman aged 30 years (fig 7) the enlargement of the right lower limb was very striking Amongst their chief findings by X ray examination was the presence of local bone changes which in the radiograms resembled *subperiosteal and*

cortical cysts Some of these cysts were bridged over by a thin layer of bone so that they could be termed cortical instead of subperiosteal Some of them could not have been felt by ordinary palpation but others formed tumours projecting from the bone



FIGS 6 and 7—*Neurofibromatous elephantiasis and periosteal neurofibromatosis* Illustrations showing enlargement of one limb from the articles by B Brooks and E P Lehman (1924) and E P Lehman (1926) by their kind permission Fig 6 is Case 2 of Brooks and Lehman a boy aged 12 years whose (affected) left leg is obviously longer than his right leg Fig 7 is Lehman's Case 8 a woman aged 30 years with enlargement of the right lower limb I heard from Prof Lehman that this case was subsequently found to have multiple tumours within the dura mater at several spinal nerve levels

Their explanation of the changes if I may express it in slightly different terms to those used in their description is that when a periosteal nerve becomes neurofibromatous a certain amount of reaction is set up as if by an infection and processes of bone destruction and regeneration follow If periosteum covers the neurofibromatous tumour a thin shell of bone is formed over the tumour which then appears in the radiogram as a subperiosteal bone-cyst If the tumour growth farther invades the shaft of the bone and is associated with more active circulation of lymph and blood the whole bone becomes more porous and plastic This may of course lead to increase in length of the bone and to bending or to irregularity if the neurofibromatous process is irregular and if a neurofibroma is so placed as to destroy an epiphysis an abnormally short bone may result [19] They compare the process to what happens in chronic inflammatory conditions in growing bones Brooks and Lehman were apparently the first to draw attention to the occurrence of periosteal neurofibromatosis and its results Similar conditions have since then probably been seen by others even if not interpreted in the same way [20] In Pusch s account of the osseous manifestation in neuro fibromatosis published in 1925 no mention is made of periosteal neurofibromatosis [21] It is interesting that in one of Lehman s later cases [22] a woman of 30 years in whom there was neuro fibromatous elephantiasis of the right lower extremity with over growth of the right innominate bone there was also a neurofibromatous pelvic tumour

In 1934 with O B Bode (*Proc Roy Soc Med* 27 638) I showed a remarkable case of neurofibromatosis in a hunchback man aged 3[illegible] He had a pendulous molluscous dermatocele on the right side of the face (neurofibromatous dermatolysis) and right buphthalmus A bony mass projected on the right temple just above the dermatolysis In a similar buphthalmic eye Murdkami (1913) found fibromatous involvement of the ciliary nerves (J H Parsons *Pathology of the Eye* 3 116) Concerning the kyphoscoliosis in this case compare H J Seddon *Proc Roy Soc Med* (1936) 29 [illegible]51 and in regard to the nature of the eye changes in such cases compare J Foster and C Polson (1934) *ibid* 27 1124 K T A Halbertsma (1935) *Arch f Ophthalmol* p 167 and other references given at the end of this paper (Notes 5 and 10)

The Present Case

When there is a diffuse mass of neurofibromatous periosteum covering a considerable area of bone we doubt whether actual penetration of the neurofibroma into the osseous cortex is necessary to give rise to hyperplasia in the underlying bone In the following case a diffuse

mass of thickened neurofibromatous periosteum covered the left tibia which was greatly thickened and curved but there was no evidence that the neurofibromatous growth had actually penetrated into the cortex of the bone We are indebted to Dr G T Stebbing of the Lambeth Hospital for clinical notes of the case and to Mr Cecil Beadle and Mr T W P Lawrence for the macroscopic and microscopic description of the specimens in the Museum of the Royal College of Surgeons to which Dr Perdrau presented them

The patient a woman (F L G) age 47 a subject of typical Recklinghausen's neurofibromatosis was admitted on January 25 1921 to the Lambeth Hospital on account of a severe accidental head injury causing a cerebral abscess from the results of which she died on February 28 1921 It was also noted that her left tibia was considerably curved in no way connected with the accident and that she had many molluscous fibromata of the skin No family history or past history bearing on the latter condition was obtained At the post mortem examination apart from the results of the accident from which she died Dr Perdrau noted

There are typical pedunculated and sessile molluscous tumours on the skin most on the trunk but also on all four limbs and face The largest is pigmented of the size of a golf ball the others are not pigmented but there are spots and patches of pigmentation especially on the trunk and thighs There are no tumours in the central nervous system or on any nerve trunks There are a few small hard tumours on the peritoneal surface of the ileum opposite the mesenteric attachment varying in size from a sago-grain to a coffee bean There are no tumours elsewhere in the internal organs (heart liver kidneys etc) excepting a doubtful one at the tip of the vermiform appendix [23] The left tibia is deformed and bent and is covered over the greater part of its length anteriorly with diffuse tumour substance resembling the semitransparent fibromata of the skin but of denser texture The tibia of the other leg is not bent

The specimens mounted at the Royal College of Surgeons are described as follows

No 3816 1 —The left fibula and outer half of the tibia from a case of Recklinghausen's disease The upper three-quarters of the anterior surface of the shaft of the tibia is covered with a layer of dense fibrous tissue ¼ inch in thickness at its middle and becoming thinner above and below The margin of the deposit is well defined and its deep surface is in contact with the bone from which it is readily detachable In the section in addition to the localized mass

described almost the whole of the periosteum of the shaft exhibits a thickening of similar character but less marked The bone adjacent to the deposit presents considerable thickening of its cortex and irregularity of its surface which however is quite smooth The tibia measures 14½ inches in length and it and the fibula exhibit a uniform curve with the convexity outwards (figs 8 9 and 10)

No 3 816 2 – The inner half of the left tibia from the same case

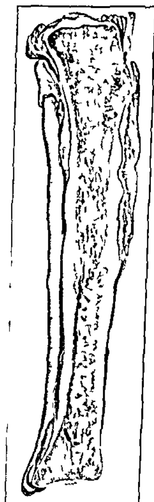


Fig 8—The present case Drawing by Mr S Steward from the left tibia and fibula (⅓ natural size) in the Museum of the Royal College of Surgeons (No 3816 1) to show the periosteal thickening (periosteal neurofibromatosis) and the irregular hyperplasia of the cortical bone of the diaphysis of the tibia

It shows similar changes the fibrous thickening of the periosteum forming a thick coating over the greater part of the shaft of the bone

Microscopic examination of the deposit on the bone shows it to consist of dense fibrous tissue with abundant cellular elements the cells being of small size and oval in form In places the cells form



FIG 9—The present case Photograph of the left tibia and fibula before splitting the tibia to show the curving of the bones and the great periosteal thickening over the upper part of the tibia We are indebted for this photograph to the Department of Applied Optics National Institute for Medical Research

narrow tracts in which the fibrous element is almost absent The structure is similar to that of the fibromata of the skin from the same case (which are preserved as No 3 074 2) but a few thickened nerves are present

No 3 074 2 – Two pieces of skin from a case of Recklinghausen's disease A number of firm fibromata varying from miliary size to



Fig 10—The present case Radiogram of the left tibia and fibula taken after death to show the bending of the bones and the great thickness and consequent opacity of the cortical bone of the main portion of the shaft of the tibia We are indebted for this radiogram to the kindness of Dr Russell Reynolds

one inch in diameter project from the surface Some of the smaller nodules are surrounded by a narrow zone of brown pigmentation and small areas of pigmentation are scattered throughout the surface of the skin

Microscopic examination shows that the tumours of the skin are fibromata their outlines are well defined but no capsule is present The texture is dense but the cellular element is abundant the cells being of small size and oval in shape The corium is somewhat sclerosed and many of the blood vessels of the papillary layer are surrounded by a narrow layer of small oval cells

In addition to these specimens Dr Perdrau has excellent micro scopic sections of the thickened (neurofibromatous) periosteum of one of the cutaneous fibromata and of one of the small tumours from the ileum The microscopic structure of the last resembles that of the others They all show typical neurofibroma as the microscopical sections in the Royal College of Surgeons do in fact in microscopical structure the various tumours examined are exactly alike (figs 11 12 and 13) Dr Perdrau also has sections of the tumours from all three localities stained by the silver reduction method for reticulin a method which he described some years ago [24] for the differentiation of reticulin from glia fibres axis cylinders etc Sections of all three tumours stain equally well for reticulin by this method

Remarks

With the exception of important observations by Brooks and Lehman this seems to be the first account explaining the deformity of an extremity or other part for instance the skull as due to peri osteal neurofibromatosis with resulting abnormal thickness or hyper plasia of the underlying bone The increased bone formation may be accounted for by comparison with the increased length of long bones caused by chronic osteomyelitis in youth as pointed out by Brooks and Lehman or long-continued chronic ulceration which causes periosteal hyperaemia As an illustration we figure the case of a boy whom I used frequently to see when in 1897 at the age of 14 years the boy was an in patient at the German Hospital The photograph (fig 14) was taken at that time by Dr J P zum Busch to whom I am indebted for it The extraordinary length of the boy s legs was due to the abnormal hyperaemia caused by chronic congenital syphilitic osteo periostitis [25] One might here also call to mind the group of cases described by Parkes Weber as manifesting haemangiectatic hypertrophy of a limb due to excessive blood supply of congenital developmental origin [26]

The present case is not really unique Besides cases figured and described by Brooks and Lehman there are various descriptions to be found in the literature on neurofibromatosis in which one of the patient's limbs was thicker and longer than its fellow These have

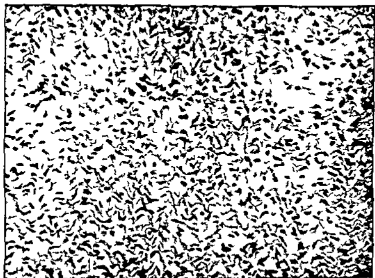


FIG 11

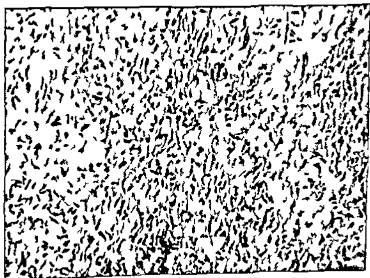


FIG 12

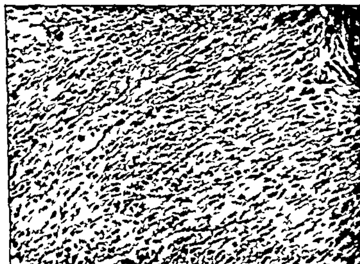


FIG 13

FIGS 11 12 and 13—The present case Photomicrographs (×240) from (fig 11) the thickened (neurofibromatous) periosteum over the left tibia from (fig 12) one of the cutaneous neurofibromatous growths and from (fig 13) one of the neurofibromatous growths of the ileum Note the somewhat coarser structure in fig 11 We are indebted for these photomicrographs to the Department of Applied Optics National Institute of Medical Research

mostly been classified as examples of neurofibromatous elephantiasis when they showed a condition of extensive plexiform neuroma or pachydermatocele of the subcutaneous tissues but in some such cases the hypertrophy or bending of the bone was probably due to overlying periosteal neurofibromatosis similar to that described in the present paper A leg amputated above the knee recently presented by Dr Maud Forrester Brown to the Museum of the Royal College of Surgeons in London showed decided increase in length as compared with its fellow and a condition of diffuse neurofibromatous elephantiasis in addition there was moderate but diffuse neurofibromatous thickening of the periosteum of the shafts of the tibia and fibula (specimens 5090 5–8)

The famous elephant man (Merrick) whom I once saw and who died at the London Hospital [27] at the age of 27 years on April 11 1890 had many deformities of the nature of pachydermatoceles as well as many bony thickenings and outgrowths There was no post mortem examination but irregular periosteal neurofibromatosis may well have played a part in his osseous deformities

Further Observations

In connexion with the various points on neurofibromatosis considered or alluded to in this paper I venture to make the following short pathological and diagnostic summary

I It is quite common in the course of ordinary medical examina

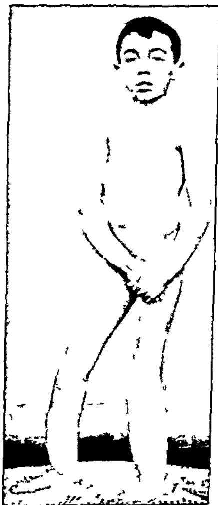


FIG 14 (for comparison)—Case of remarkable enlargement of the long bones of the legs due to congenital syphilis From a photograph taken in 1897 when the patient was aged 14 years The forearms are similarly but to a lesser degree affected This photograph for which I am indebted to Dr J P zum Busch (*see* text) is to contrast with cases of bony enlargement accompanying periosteal neurofibromatosis

tions to meet with one or two simple pigmentary or hyperchromic naevi indistinguishable from the cutaneous pigment spots of Recklinghausen's disease and to meet with one or two little molluscous fibromata of the skin These have no importance unless in association with other signs When however it is a question of the nature of a chronic non inflammatory swelling in one half of the tongue or of a loose fold of superabundant skin and subcutaneous tissue over one eye or at the side of the head they have a significance in favour of neurofibromatosis as an explanation of the condition

2 The prognosis in a case of supposed pigmentary forme fruste of Recklinghausen's disease in a child or young person should be very guarded Most cases develop later into full blown neurofibromatosis In young women pregnancy and probably also the onset of puberty may act as an excitant in the development of molluscous fibromata etc

3 The tumour like swellings due to plexiform neuroma and those which have been described as elephantiasis nervorum merge into pachydermatocele and molluscous subcutaneous fibromatous pendulous tumours and flounce like folds Changes of the kind have often been called elephantiasis (neurofibromatosa) since the term elephantiasis was formerly applied to any chronic deforming and unsightly enlargement of an extremity or other part of the body The term dermatolysis or dermolysis looseness or loosening of skin should be avoided in regard to pachydermatoceles and the kindred folds as it leads to confusion with the very rare condition of congenital generalized elastic skin in which the skin is abnormally loosely attached to the parts beneath it [28] so that the skin of the chest for instance can be drawn out in a fold to cover the face but when released at once owing to its inherent normal or over normal elasticity retracts to its natural position

4 Tumour like swellings of the above elephantiastic class including plexiform neuroma pachydermatocele diffuse molluscous subcutaneous connective tissue tumours and folds are often associated with hyperostosis (hyperplasia) of the underlying bones whether of the limbs or head or elsewhere There has been great confusion in regard to the explanation of the cranial deformities sometimes associated with such neurofibromatous swellings and pachydermatocele folds of the face and scalp and likewise with regard to the association in other parts of elephantiastic swellings with local osseous hyperplasia

5 In the above-described case of the woman F L G the osseous

hyperplasia of the left tibia was associated with irregular diffuse neurofibromatous thickening of the periosteum covering it and with bending of the shaft of the bone It remains to be seen how often a similar condition of neurofibromatous diffuse thickening of the periosteum will be found in cases of gross osseous hyperplasia and deformity of an extremity or of the face or skull in cases of neurofibromatosis The description by Brooks and Lehman of subperiosteal and cortical cysts and other changes in the bones found by X ray examination in cases of neurofibromatosis constitutes a landmark in the history of our knowledge of the subject

6 As causes of chronic thickening of nerve trunks besides leprosy there are two of congenital developmental nature (*a*) the exceedingly rare familial hypertrophic neuritis in which the thickening is said to be of the sheath of Schwann [29] (*b*) diffuse neurofibromatosis of nerve trunks The latter which is only a diffuse and more *generalized variety of multiple neurofibromata (discrete neurofibromatous tumours)* of nerve trunks may be very widely distributed it may affect not only the spinal nerves of the extremities body and neck and probably the head but also the sympathetic and vagus nerves and the visceral nerve plexuses e g about the heart and aorta

7 Amongst the causes of enlargement notably in bone length of a single extremity two rare causes of a congenital developmental nature should be better recognized (*a*) the haemangiectatic hypertrophy of an extremity (Parkes Weber) already alluded to [26] and (*b*) the enlargement due to neurofibromatosis The latter is generally accompanied by plexiform neuroma (plexiform neurofibroma) or neurofibromatous pachydermatocele of the soft parts of the extremity both plexiform neuroma and pachydermatocele when in extreme degree *are often spoken of as neurofibromatous* elephantiasis but it will probably be found that more less diffuse neurofibromatous thickening of the periosteum is nearly always likewise present in these cases to account for the bony hyperplasia as it was in the amputated leg to which I have already referred under Remarks *(see abo e)*

In cases of both these rare classes the bony hyperplasia is probably intimately connected with excessive blood supply In the haemangiectatic cases the increased *blood supply is the direct result of the* primary (developmental) vascular abnormality in the periosteal neurofibromatous cases it is secondary and possibly a reactionary manifestation as it of course is in the cases of syphilitic hypertrophy of extremities to which I have alluded

8 Besides syphilis tuberculosis and leprosy three possible though rare causes of chronic periosteal thickening should be remembered

(A) Secondary osteo arthropathy of Pierre Marie The periosteal thickening in these cases commences in and affects especially the terminal portions of the extremities notably the phalanges and meta carpal and metatarsal bones It is always accompanied by clubbed fingers

(B) Periosteal lymphogranulomatosis This is apparently limited to the vertebral column is probably of more frequent occurrence than has been suspected in late cases of lymphogranulomatosis maligna (Hodgkin s disease) especially when the para aortic and retroperi toneal lymphatic glands are much involved Clinically its presence should be suspected in such cases when bilateral radiating lumbar and sciatic pains are complained of and of course when paraplegic symptoms are commencing which may be asymmetrical at first The lymphogranulomatous periosteal thickening seems to commence symmetrically in front of or at the sides of the bodies of the vertebrae about the level of the diaphragm and then tends to spread round so as to involve the spinal canal and the epidural fat It has been specially considered by me in connexion with the occurrence of cauda equina symptoms and paraplegia in Hodgkin s disease [30] Incidentally the lymphogranulomatous process like the neurofibro matous process may become sarcomatous [31]

(C) Periosteal neurofibromatosis which has constituted the main subject of the present paper Although undoubtedly it was present in some earlier reported cases it was hardly recognized as such if recognized at all until Brooks and Lehman drew attention to the subject in 1924 and recognized its pathological and clinical interest and importance As I have endeavoured to explain in this paper more or less periosteal neurofibromatosis with its consequent hyper aemia is probably present in all the cases roughly grouped together as neurofibromatous elephantiasis of limbs especially those which show definite excess in bone length (compare conclusions 4 and 5) Such cases are apparently nearly always unilateral

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[2] Adrian C *Centralbl f d Gren geb d Med u Chir* Jena 1903 6 465 514 A Puech Les manifestations osseuses dans la neurofibromatose

Paris Med 1925 57 502 Laignel Lavastine and Valence *Bull et Mem de la Soc med des hop de Paris* 1926 Ser iii 50 273

[3] Brooks B and Lehman E P The Bone Changes in Recklinghausen s Neurofibromatosis *Surg Gynecol and Obstet Chicago* 1924 38 587 95 Case 4 Laignel Lavastine and Dauptain (*Bull et Mem de la Soc med des hop de Paris* 1924 Ser iii 48 1163) recorded the case of a man aged 37 years with typical complete Recklinghausen s disease and a spina bifida occulta in the lumbar region his daughter had a pigmentary incomplete form of the disease

[4] Weber F Parkes Cutaneous Neurofibromatosis 1941 25 431 *Proc Roy Soc Med* Lond 1925 (Clin Sect) 18 1 4 The patient had a left lateral (suprazygomatic) soft fibromatous fold of skin of the nature of a pachydermatocele as sometimes met with in cases of neurofibromatosis I mistook this for a meningocele

[5] *See* Weber F Parkes The Relations of Capillary Haemangiectatic Naevus and Naevus Anaemicus to the Nervous System *Brit Journ Derm and Syph* 1929 41 221 Cf Wakeley and Weber *Internat Clinics* 1936 eries 46 1 144 In regard to abnormal conditions of the eye in neurofibromatosis *see* T Van der Hoeve Eye Diseases in Tuberose Sclerosis of the Brain and in Recklinghausen s Disease *Trans Ophthalm Soc United Kingdom Lond* 1923 43 534 and H Fischer *Dermat Zeitchr Berlin* 1942 42 143 68 For neurofibromatosis of the choroid *see* Blackwood and Cookson *Brit Journ Ophth* 1941 25 431 For unilateral buphthalmus in neurofibromato is *see* Weber F Parke and Bode O B 1934 *Proc Roy Soc Med* 27 638 For hereditary combination of neurofibromatosis with epidermolysis bullosa *see* Curtius F and Strempel R *Derm Zeitschr* 1928 51 401

[6] *In regard to the possible relation of neurofibromatosis to sclerotic or* gliomatous patches in the central nervous system and tuberous sclerosis *see* Cristin E and Naville F A propos des neurofibromatoses centrales *Annales de Med* Paris 1920 8 30 50 also the following articles for reference to which I am indebted to Dr Macdonald Critchley Gamper E *Journ f Psych u Neurol* Leipz 1929 39 39 Bielschowsky and Rose *ibid* 1928 35 42 Bielschowsky Ueber tuberose Sklerose und ihre Beziehungen zur Recklinghausenschen Krankheit *Zeitschr f d ges Neurol u Psych* Berlin 1914 26 133 Orzechowski and Nowicki Neurofibromatose und Sclerosis tuberosa (Neurofibromatosis universalis) *ibid 1912 11* 237 Schnyder P Ueber Gliom Gliose und Gliomatose und ihre Beziehungen zur Neurinomatosis *Schweizer Arch f Neurol u Psych* Zurich 1928 23 116 *See also* Critchley and Earl *Brain* 1932 55 311

[7] Weber F Parkes *Brit Journ Dermat* Lond 1905 17 276 *ibid* 1909 21 49 *Proc Roy Soc Med* (Sect of Derm) 1927 30 22 For many references to the literature on Pigmentary Incomplete Forms of Recklinghausen s Disease *see* Weber F Parkes *Med Press and Circ* Lond *1925 170* 416 19 *See also* Wise F and Eller J J *Journ Amer Med Assoc* Chicago *1926 86 86 Eller J J Arch Derm and Syph ibid 1928 17 648* Grenet H Ducroquet R Isaac Georges P and Mace M *Presse medicale 1934* 42 2060 (Forme fruste pigmentaire et osseuse de la neurofibromatose")

[8] Soldan Ueber die Beziehungen der Pigmentmaler zur Neurofibromatose *Arch f klin Chir Berlin* 1899 59 261 96

[9] Cf Sutton R L Fibroma Molluscum Gravidarum *Amer Journ Med Sci* Philad 1914 147 419 On the effects of pregnancy in neurofibromatosis *see also* Moreira *Gynecol et Obstet Sept 1930* p 229

[10] For many references on the association of Recklinghausen s disease or one of its incomplete forms with acromegaly Addison s disease or an incomplete form of dystrophia adiposogenitalis (Frohlich s syndrome) and on

Leschke s dystrophia pigmentosa *see* Weber F Parkes *Med Press and Circ* Lond 1925 170 416 19 Cornil Kissel and Beau (Soc de Neurol Paris March 6 1930) recorded destruction of the sella turcica in a case of hereditary neurofibromatosis In regard to neurofibromatosis of the orbit *see* Morgan O G *Proc Roy Soc Med* 1935 28 189 and Neumann H *Derm Wochenschr* 1938 107 1481 For neurofibroma of the third cranial nerve *see* Elder N G *Journ Path and Bact* 1941 52 766 *see also Brit Med Journ* 1940 2 839 cf Pugh *Proc Roy Soc Med* 1946 39 695

[11] *See* Abbott and Shattock *Trans Path Soc Lond* 1903 54 231 Spencer and Shattock *Proc Roy Soc Med* (Sect Path) Lond 1908 1 8 Weber F Parkes Neurofibromatosis of the Tongue *Brit Journ Child Dis Lond 1910 7 13 Oddy H M Proc Roy Soc Med (Sect Study of Dis in* Children) Lond 1929 22 93 *See also* Hayashi A Makroglossia congenita neurofibromatosa *Deut Zeitschr f Chir* Leipz 1912 118 456 and the cases quoted by him On the analogous condition in the *lip* (hemimacrocheilia neurofibromatosa) *see* Rolleston J D and Macnaughton N S *Proc Roy Soc Med* (Clin Sect) Lond 1911 4 114 In neurofibromatous hypertrophy of half of the tongue nerve cords are not always distinctly felt—cf W Russell Brain s case (which I had the privilege of examining) reported in *Brain* Lond 1928 51 113 Some cases of diffuse bilateral or unilateral hypertrophy of *gums* are doubtless of neurofibromatous nature (though not plexiform neuroma) at least the hereditary ones such as those in the group of familial molluscous fibromata cases described firstly by John Murray in 1873 (*Med Chir Transactions* Lond 1873 56 235) and later by Whitfield A and Robinson A H (*ibid* 1903 86 293) On this subject compare also the *cases of unilateral hypertrophy of gums associated with other* abnormalities collected by Sir G M Humphry in Selected Essays and Monographs New Syd Soc Lond 1901 173 279 36 In the case of a boy aged 4 years described by Marfan A B and Schmitte under the heading Adeno lymphocèles et lymphangiomes congénitaux avec taches pigmentaires généralisées *sans molluscum et sans neurofibromes* (*Bull de la Soc de Pédiatrie de Paris* 1926 24 269) I would suggest that the right sided hemihypertrophy of the tongue was more probably of neurofibromatous than of lymphangiomatous nature Wigley and Muende showed (*Proc Roy Soc Med* 1945 38 505) a girl aged 15 years with plexiform neuroma of the tongue *See* Gray A M H *Proc Roy Soc Med* (Sect Derm) Lond 1929 22 38 the patient a boy aged 15 with Recklinghausen neurofibromatosis had a great nodular enlargement of the median and ulnar nerves in both arms In regard to oral lesions in neurofibromatosis *see also* Dillon C *Brit Dent Journal* 1947 72 167 Worster Drought and Hill *Proc Roy Soc Med* 1930 23 171 Martin and Grove *J Amer Med Ass* 1941 117 1535 Hankey G T *Proc Roy Soc Med* 1933 26 959 (with palatal tumour)

[12] Cf A E Barker s case *Trans Med Soc Lond* 1917 35 3 6 I was able to palpate the swelling myself on two occasions *See also* Bell G and Inglis K *Med J ... Australia* 19 5 2 4 3 a case of plexiform neuroma associated with giant growth of one finger

[13] In regard to the adjective elephantiastic or elephantiasic cf Esmarch and Kulenkampff monograph *Die elephantiastischen Formen* Hamburg 1885 Cf also Corner H *Proc Roy Soc Med* 1937 35 1 39 Savatard L *Brit Journ Derm* 1931 93 414

[14] Compare remark by Weber F Parkes on a complicated case of neurofibromatosis with a symmetrical facial hypertrophy as shown by W Russell Brain at the Neurol Sect of the Roy Soc Med on November 10 1927 as reported in *Brain* Lond 1928 51 113 Various of the earlier cases of neurofibro

matosis associated with partial cranial hyperostosis were referred to in a paper by Weber F Parkes *Brit Journ Child Dis* Lond 1910 7 13 16 Authors have mentioned and discussed not only the irregular areas of cranial hyperostosis sometimes connected with neurofibromatous conditions of the soft parts covering them but also patches of thinness or local atrophy or decalcification that have occasionally been demonstrated by X ray examination of the skull in patients with Recklinghausen s disease Cf Brooks and Lehman (1924) and Lehman (1926) both referred to further on and Stahnke E *Deut Zeitschr f Chir* Leipz 1922 168 6 On the whole subject of the cranial changes in neurofibromatosis and for references on the subject *see also* Winkelbauer E *ibid* 1927 205 230 257 also Weber F Parkes and Bode O B 1934 Recklinghausen s Neurofibromatosis with Unilateral Buphthalmus and Multiple Changes in the Face and Skull *Proc Roy Soc Med* 27 1638 (striking illustration)

[15] Cf Banerjee D N and Christeller E Ueber die gastro intestinalen und andere seltenere Lokalisationen der Neurofibromatosis *Virchow s Archi f Path Anat u Physiol* Berlin 1926 261 50 67

[16] In a case of generalised neurofibromatosis under Moynihan (*Lancet* Lond 1901 1 78) there was a neurofibromatous tumour of the vagus nerve In a case described by Preble R B and Hektoen L (*Amer Journ Med Sci* Philad 1901 121 1) there were tumours of the vagus and cervical sympathetic nerves and their branches in their illustration of the affected vagus and sympathetic nerves about the base of the heart and large vessels in the thorax a subpericardial neurofibromatous nodule is also shown In an annotation in the *Lancet* (1929 2 1364) we read that amongst the recent additions to the Museum of the Royal College of Surgeons there are specimens of Recklinghausen s disease illustrating the remarkable convoluted masse of enlarged nerves and the extensive involvement not only of the peripheral nerves but also of the great plexuses the vagi and other cranial nerves and the sympathetic nervous system We find that the last specimens alluded to are Nos 5090 1 5090 2 5090 3 and 5090 4 (all from one case and presented by the London School of Medicine for Women) In regard to involvement of the stomach *see* Barber T H T *Trans Med Soc Lond* 1932 55 95 and Aksel *Brit Med Journ* 1944 2 309 Re neurofibromatous epulis *see* Hickman E M *Journ Path and Bact* 1932 35 146 For neurofibromatosis of the urinary bladder *see* Chalkley and Bruce *Journ Pediat* 1942 20 632

[17] Gould E P The Bone Changes occurring in von Recklinghausen s Disease *Quart Journ Med* Oxford 1918 11 221 Regarding spontaneous fractures in neurofibromatosis I have heard of a case in England and see Armelin G *les dystrophies osseuses de la neurofibromatose* Paris 1933 Pugh s case of kypho scoliosis in a girl with hereditary neurofibromatosis (*Proc Roy Soc Med* 1930 23 1327) showed involvement of several vertebrae

[18] Brooks B and Lehman E P The Bone Changes in Recklinghausen s Neurofibromatosis *Surgery Gynecology and Obstetrics* 1924 38 587 95 Uhlmann E and Grossman A (*Arch Int Med* 1940 14 225) record two cases of neurofibromatosis one showing marked cystic changes in the mandible the other enlargement and bowing of the tibia with elephantiasis nervorum — also osteoporosis and deformity of cervical vertebrae in the region of a rapidly growing neurofibroma Cf Tanner s case *Proc Roy Soc Med* 1947 40 47

[19] For references to older literature on the connexion of lengthening or shortening of extremities with neurofibromatosis *see* Stahnke Ueber Knochenveranderungen bei Neurofibromatose *Deut Zeitschr f Chir* Leipz 1922 168 6

[20] Cf Babinneix Touraine and Pollet *Bull et Mem de la Soc med des hop de Paris* 1925 series iii 49 1601 Tixier (Lyon) report in *Presse medicale* Paris 1925 33 1689 and other scattered observations

[21] Puech A *Paris medical* 1925 57 507

[22] Lehman E P Recklinghausen s Neurofibromatosis and the Skeleton *Arch of Derm and Syph* Chicago 1926 14 1 8

[23] Cf Hoey T Recklinghausen s Disease associated with Fibroma of the Appendix *Brit Med Journ* 1928 2 490

[24] Perdrau J R *Journ Path and Bact* Edinb 1921 24 117

[25] The case was described and figured by Mr R W Parker in his article on Syphilis in Gould and Warren s *International Text book of Surgery* (1900 2 480) and was referred to by F Parkes Weber in A Note on Congenital Syphilitic Osteitis Deformans *Brit Journ Child Dis* Lond 1908 5 83 The patient when seen by Dr zum Busch in 1913 sixteen years after the photograph was taken had no signs of active syphilis but the bones were of course still somewhat deformed

[26] *See* Weber F Parkes Haemangiectatic Hypertrophy of Limbs *Brit Journ Child Dis* Lond 1918 15 13 Gray A M H Haemangiectatic Hypertrophy (Parkes Weber) *Proc Roy Soc Med* (Sect Derm) Lond 1928 21 65 Various other examples of this rare congenital developmental abnormality are referred to in these papers and I have seen an account of the condition in France in which it is stated to be apparently commoner in England! The condition has also been termed in Argentina the Parkes Weber and Klippel syndrome For a review of the whole subject *see* Reichenheim P P *St Barth Hospital Journal* London 1943 wartime series 4 53

[27] *See* the illustrations of the elephant man in the *Brit Med Journ* 1886 2 1188 1890 1 916 1923 1 335 *See also* Treves F A Case of Congenital Deformity *Trans Path Soc* Lond 1885 86 494

[28] *See* Weber F Parkes Chalasodermia or Loose Skin *Urol gic and Cutaneous Review* St Louis (Missouri) 1923 27 407 For cutis laxa in connexion with the Ehlers Danlos syndrome *see Weber* F Parkes *Brit Journ Dermatology* 1936 48 609

[29] There are two types that of Dejerine and Sotta and that of Pierre Marie I saw one of Dejerine s original familial cases in Paris about 1923 Dr Macdonald Critchley has pointed out to me that familial hypertrophic neuritis is pathologically related to neurofibromatosis according to the work of Bielschowsky *Journ f Psych u Neur* Leipz 1923 29 182 Verocay J (Zur Kenntnis der Neurofibrome *Beitr path Anat u Allg Path* Jena 1910 48 1 69) thought that the tumours of Recklinghausen s disease for which he suggested the term neurinomata arose from the cells of the sheath of Schwann but this view has been only partially accepted More recently S H Gray in a paper on The Histogenesis of Recklinghausen Disease (*Arch of Neurol and Psych* Chicago 1929 22 91) for reference to which I am indebted to Dr Perdrau described two cases in both of which a fibro sarcomatous change had occurred In one of these cases serial microscopic sections showed the tumour arising not from the cells of the sheath of Schwann but from the perineural connective tissue

[30] Weber F Parkes Paraplegia and Cauda Equina Symptoms in Lymphogranulomatosis Maligna *Quart Journ Med* Oxford 1923 17 1 5 Lymphogranulomatosis Maligna and Leukaemia *International Clinics* Philad 1926 Ser 36 1 127 136 Weber and Bode Abdominal Lymphogranulomatosis Maligna and Lymphogranulomatous Infiltration of the Epidural Fat *Lancet* Lond 1927 2 806 Periosteal thickening of the vertebrae may however be present without cauda equina symptoms or paraplegia and these latter symptoms may occur in cases of

lymphogranulomatosis maligna without periosteal thickening—cf above references and also Fast and Lightwood Lancet Lond 1937 2 801 and Carslaw and Young *Glasgow Med Journ* 1927 108 193 For a somewhat analogous symmetrical periosteal elevation over various bones in lymphatic leukaemia and aleukaemic lymphadenosis (due to subperiosteal leukaemic infiltration) *see* Taylor H K Periosteal Changes in a Case of Lymphatic Leukaemia *Radiology* 1926 6 523 5

[31] Cf Weber F Parkes La lymphogranulomatose maligne ou granulome de Hodgkin et la question du sarcome de Hodgkin *Strassbourg medical* 1926 84 255

XXXVII

HEPATOMEGALIA GLYCOGENICA

FRANK SARGENT

Synonyms — Glycogen disease glycogen storage disease hepato nephro-megalia glycogenica cardiomegalia glycogenica thesaurismosis glycogenica von Gierke s disease

History — This rare disease of children was described by several authors before von Gierke whose name is often attached to it reported 2 cases with post mortem findings

In 1921 Wagner and Parnas of Vienna reported the case of a 4 year old girl who had enlargement of the liver from the age of 3 months with ketonuria but no glycosuria Sugar appeared in the urine after a diet rich in carbohydrate and later she developed diabetes mellitus Consequently this case is not exactly typical of the condition

Worster Drought (1923) in this country examined a 10 year-old girl in 1920 and found enlargement of the liver with ketonuria and acetone in the breath he showed her before the Section for the Study of Disease in Children of the Royal Society of Medicine London in 1923 as a case of enlarged liver with persistent acetonuria and diaceturia (fig 1) The liver firm and smooth was felt 3 in below the costal margin The spleen was not palpable The urine contained no sugar but acetone and diacetic acid were both persistently present The girl had a profound dislike for and intolerance of fats The parents stated that between the ages of 1 and 5 years she had failed to grow had shown swelling of the abdomen had convulsions for a time and also cyclical vomiting Hepatic efficiency tests gave normal results The Wassermann reaction was negative It was suggested that this case was a case of constitutional metabolic disorder mainly involving the liver Shown again in 1935 the patient had evidently outgrown her disease the liver was no longer enlarged and there were no symptoms except that she continued to show occasional acetone in the breath and urine She was then 5 ft 6½ in in height and weighed 9 st 6 lb A brother had died of kidney disease at the age of 3 years and was said by a doctor to have had enlarged liver and spleen

Snapper and van Creveld of Amsterdam (1928) reported the case of a boy aged 7 years his liver had been enlarged since he was 3 months old and he also showed ketonuria without glycosuria in addition to cyclic vomiting

In 1929 von Gierke (Germany) published the post mortem findings in 2 cases Both showed gross *enlargement of the liver and in one* case the kidneys also were enlarged in both cases the liver and kidneys were laden with glycogen which was clearly the cause of the enlargement

Since this date many further cases have been reported notably those by Ellis (1933–34) in London which showed a familial incidence in two instances (fig 2) and cardiac enlargement demonstrated at autopsy in one case Pompe (1932) reported a case of cardiac enlargement due to glycogen accumulation with autopsy notes An excellent historical review with full bibliography was given by Atkinson in the *British Journal of Children s Diseases* in 1939

Pathology –The disease consists essentially of an abnormal accumulation of glycogen in the tissues especially the liver although *other organs may be involved* This greatly increased storage of glycogen results from a congenital defect in the carbohydrate enzyme system whereby the normal conversion of glucose into glycogen is *prevented* and likewise *the mobilization of glucose from glycogen* The defect does not appear to be of the glycogenolytic enzyme itself nor is the glycogen abnormally stable for it can be broken down into glucose by the addition of a mash of normal liver the conclusion therefore is that the missing factor is one which forms a link between glycogen and the enzyme (*Lancet* 1948 **1,** 296) Laevulose and galactose are not affected by this discrepancy for they are readily converted into glycogen but the glycogen so formed does not *yield* glucose (Mason and Anderson 1941) The accumulation of glycogen in the tissues somewhat resembles the abnormal storage of lipoids in *Gaucher s disease and in the Niemann Pick disease but in* von Gierke s disease the glycogen is found in the parenchymatous cells while in the lipoidoses the lipoids are in the reticulo-endothelial cells Other tissues sometimes involved are heart kidneys muscle and brain The spleen is never enlarged but the enlarged left lobe of the liver has sometimes been clinically mistaken for the spleen In 21 cases that came to autopsy the organs affected were as follows liver alone 5 liver and heart 8 liver and kidneys 4 heart alone 3 liver kidneys and heart 1 The liver was usually very large and in one of von Gierke s cases it weighed 2 730 grammes While glycogen is difficult to *demonstrate in the normal liver because* it is rapidly destroyed by ferments after death in this condition it is readily stained with Best s carmine stain and is demonstrable in the clear distended parenchymatous cells of the liver at least twenty four hours

after death There is no decrease in glycogen content after keeping the liver in the ice box for a week but there is a marked decrease on mixing with normal liver which supplies the adequate enzyme complex (Boyd) The ketosis which is so constantly found was formerly thought to be caused by the incomplete combustion of fats in the presence of a low blood sugar It is now believed however that ketone bodies are normally formed in the liver and utilized by the tissues but that when fat katabolism is excessive the tissues cannot cope with the additional ketones which then appear in the urine and breath This is not dependent on any change in carbohydrate metabolism The normal sequence is glucose glycogen glucose but here it is glucose fat $\left\langle \begin{matrix}\text{glucose}\\ \text{ketones}\end{matrix}\right.$



Fig 1 —C W r ter Drought s case at the age of 10 showing pr tuberance of abdomen due to the enlarged liver

The theory that undue stability of glycogen through linkage with protein is the reason for glycogen storage has not been proved and has been discarded. Dyspituitarism has been invoked as the centre of the derangement of carbohydrate metabolism but here also proof is lacking.

Symptomatology – The disorder is a congenital and sometimes familial disease which exists from birth or an early age. It affects either sex. First cousin marriages in some of the affected families suggest that it may be transmitted as a Mendelian recessive (Ellis). The complaint for which the parents generally bring the child to the doctor is *painless enlargement of the abdomen* (fig 1). On examina

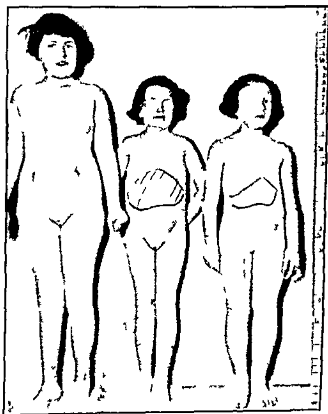


FIG 2—Familial Glycogenic Hepatomegaly
(Reproduced by the courtesy of Professor R W B Ellis)
The B Family

Control	Olive	Aline
(10 1/2 years)	(13 1/2 year)	(10 years)

tion the enlarged liver is found to be the cause of this swelling and it may reach as far down as the pelvis it is firm and smooth without tenderness It may fill both sides of the abdomen and the left lobe has been mistaken for the spleen Growth is usually stunted the child appears to grow up round its liver Infantilism has often been noted in older patients A smell of acetone in the breath draws attention to the ketosis which is invariably present analysis reveals the presence of acetone and diacetic acid in the urine but no sugar Intolerance of fats is a common complaint Convulsions have been reported and are probably due to hypoglycaemia although it is possible that deposits of glycogen in the brain are the cause Obesity is sometimes met with and this together with the occurrence of infantilism has led to the incrimination of the pituitary as the source of the dyscrasia Cardiac enlargement with or without enlargement of other organs has been demonstrated in some cases and to this association the term cardiomegalia glycogenica has been applied Sudden death may occur from this cause Delay in storage of glucose is shown by the abnormal sugar curve with the glucose tolerance test while the difficulty in the mobilization of glucose is shown by the lack of response to an injection of adrenaline Biochemical tests show hypoglycaemia increased blood glycogen (more in the red blood cells than in the serum) and increased blood cholesterol Among other unusual signs and symptoms reported are facial telangiectases myxoedema with macroglossia xanthoma pigmentation and osteoporosis

Prognosis – In the absence of intercurrent disease the patient may lead a normal healthy life indeed the disease may undergo spontaneous cure Worster Drought s original ca e is alive and well today at the age of 39 (personal communication) In many cases however there seems to be a poor resistance to infection and most of those which have come to autop y have died from intercurrent infections such as influenza pneumonia etc As stated previously cases with cardiomegaly may die suddenly

Treatment – These children should be protected from infection as far as possible A high carbohydrate diet with limited fats suits them be t Pituitary extracts have been tried without much success In a few cases X ray therapy has been applied to the enlarged liver but the reported results are variable

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—— and Weber F Parkes (1933) *Brit Med Journ* 1 403

XXXVIII

HAEMANGIECTATIC HYPERTROPHY OF LIMBS AND HAEMANGIECTATIC HEMIHYPERTROPHY

F PARKES WEBER

At the beginning of this century a great many cases of developmental enlargement of limbs were shown at the Society for the Study of Disease in Children at the Clinical Society of London and later at the corresponding Sections of the Royal Society of Medicine into which the first two societies were merged Usually one or both lower limbs were affected and most of the cases belonged to what I now prefer to term the Nonne Milroy Meige class of chronic developmental oedema (the terms trophoedema and lymphoedema are unsatisfactory) often leading to one form of non tropical non filarial elephantiasis In all these cases the enlargement is confined to the soft parts and is not associated with any increased length of the affected limb Often more than one member of the family are affected (dominant Mendelian heredity)

But occasionally cases of another class of congenital or developmental enlargement of limbs were shown – usually a single upper or lower limb (for a possible exception – both lower limbs – *see* L Ombredanne *Rev d'Orthoped* 1914–1917 5 431) without any oedema of the soft parts and (in typical cases) always accompanied by increased length of bones no history of anything similar in other members of the family can usually be obtained In nearly all cases there is obvious enlargement of arteries or veins or both (phlebarteriectasis) in the affected limb and sometimes there may be a developmental communication between arterial and venous channels producing symptoms similar to those of traumatic arteriovenous aneurysm There are often telangiectatic or other vascular hamartomata – and sometimes other forms of hamartomata – in the affected extremity or other parts of the body So-called congenital varicose veins may constitute a feature in this class of cases These cases differ from the remarkable cases of monstrous enlargement (*true* gigantism) of hand feet fingers or toes by the absence of special haemangiectasis in the latter class in which enlargement of nerve trunks may be enormous Telangiectatic hypertrophy of limbs is a developmental dysplastic condition and is naturally not very rarely associated with other dysplastic errors of development A G Watkins (*Brit Med Journ* 1941 2, 849) recorded a case of congenital arteriovenous anastomosis and haemangiectatic hypertrophy with lymphangiectasis and intermittent lymphorrhagia In

the case of a man aged 33 shown by D F Bedford (*Proc Roy Soc Med* 1938 **21,** 557) the haemangiectatic hypertrophy (with phlebarteriectasis) of the left arm was associated with coarctation (stenosis) of the aortic isthmus – an example of the association of two kinds of congenital or developmental abnormality in the circulatory system analogous for instance to the association of coarctation of the aorta with congenitally weak spots in the arteries at the base of the brain leading to developmental (not necessarily congenital) aneurysms

The primary urge (whatever may be its cause) to haemangiectatic hypertrophy of limbs is not likely to be a local developmental enlargement of blood vessels The enlargement of blood vessels and the enlargement in length of the affected limb are more probably both due to a primary urge of unknown nature though increase in size of nutrient arteries of bones can probably lead to increased nutrition and hence increased growth of bones F Parkes Weber (*Proc Roy Soc Med* 1932–1933 **26,** 52) showed a boy aged 1 year and 4 months with developmental hypertrophy of the right lower limb which could have been included as one of haemangiectatic hypertrophy but there was no obvious haemangiectasis of any kind in the affected limb It was therefore suggested that in cases termed developmental haemangiectatic hypertrophy the hypertrophy might be due not to a primary haemangiectatic condition but to an unknown urge which causes both the haemangiectasis and the hypertrophy

My original paper on the whole subject which I will reprint here was published in the *British Journal of Children s Diseases* (1918 **15,** 13) under the heading Haemangiectatic Hypertrophy of Limbs – Congenital Phlebarteriectasis and So called Congenital Varicose Veins –

There is a kind of congenital or developmental hypertrophy and dilatation of arterial and venous trunks especially those of one of the upper limbs – a tumour like haemangiomatous overgrowth in the vascular system which may be I think roughly compared to conditions of plexiform (also called vermicular or cylindrical) neuroma (German Rankenneurom) – one kind of elephantiasis nervorum – in the nervous system Both the arteries and the veins of an extremity may be involved and sometimes the communication between the arterial channels and the venous channels may be so free that a definite kind of thrill or pulsation rhythmical with the heart s contractions is transmitted to the veins as in cases of arterio venous anastomosis of traumatic origin The condition is

best termed congenital or developmental phlebarteriectasis and in its most typical forms is seen confined to one of the upper or lower extremities but cirsoid aneurysms and plexiform haemangiomata (plexiform racemose or anastomotic aneurysms – German Ranken angiom) as met with about the scalp and face are probably some times of the same nature

When (as in Bockenheimer s case – *see* further on) in one of the extremities the phlebarteriectasis is almost confined to the veins (congenital or developmental phlebectasis) i e when the arteries are only slightly affected in comparison with the veins we get an example of one kind of the rare so-called congenital varicose veins

Phlebarteriectasis may be associated with ordinary kinds of capillary or venous angiomata just as in some cases of von Reckling hausen s disease (neurofibromatosis) plexiform neuromata may be associated with ordinary neurofibromata of the skin and subcutaneous tissue

An extremity affected by congenital or developmental phleb arteriectasis is practically always longer than its fellow and this increase in size of the limb has sometimes been spoken of as gigan tism or giant growth But in cases of typical true gigantism or giant growth (as met with especially in one or two fingers or toes) the hypertrophy is much greater and the blood vessels are not specially involved that is to say not more than the other tissues of the hyper trophied part For the hypertrophy of a limb connected with congenital or developmental phlebarteriectasis I now prefer the term angiectatic or haemangiectatic hypertrophy

Cases of this kind of hypertrophy of limbs have been described under various headings and they should be especially differentiated from cases of the type of hypertrophy met with in hemihypertrophy The latter type may I believe be limited to one of the four limbs or sometimes the lower limb on one side of the body may be affected together with the upper limb on the other side (so-called crossed hemihypertrophy) Hemihypertrophy is not rarely associated with the presence of ordinary kinds of haemangiomata but is not associated with typical phlebarteriectasis that is to say it is not associated with excessive congenital or developmental hypertrophy and dilatation of the arterial and venous trunks in the affected part [1]

[1] I now think that some of these cases of hemihypertrophy are of the same nature as developmental haemangiectatic hypertrophy of limbs – compare my remarks (above) on developmental hypertrophy (in length) of limbs without obvious haemangiectasis of any kind in the affected extremity – F P W March 1 1949

P*

the case of a man aged 33 shown by D E Bedford (*Proc Roy Soc Med* 1938 **21,** 557) the haemangiectatic hypertrophy (with phlebarteriectasis) of the left arm was associated with coarctation (stenosis) of the aortic isthmus – an example of the association of two kinds of congenital or developmental abnormality in the circulatory system analogous for instance to the association of coarctation of the aorta with congenitally weak spots in the arteries at the base of the brain leading to developmental (not necessarily congenital) aneurysms

The primary urge (whatever may be its cause) to haemangiectatic hypertrophy of limbs is not likely to be a local developmental enlargement of blood vessels The enlargement of blood vessels and the enlargement in length of the affected limb are more probably both due to a primary urge of unknown nature though increase in size of nutrient arteries of bones can probably lead to increased nutrition and hence increased growth of bones F Parkes Weber (*Proc Roy Soc Med* 1932–1933 **26,** 52) showed a boy aged 1 year and 4 months with developmental hypertrophy of the right lower limb which could have been included as one of haemangiectatic hypertrophy but there was no obvious haemangiectasis of any kind in the affected limb It was therefore suggested that in cases termed developmental haemangiectatic hypertrophy the hypertrophy might be due not to a primary haemangiectatic condition but to an unknown urge which causes both the haemangiectasis and the hypertrophy

My original paper on the whole subject which I will reprint here was published in the *British Journal of Children s Diseases* (1918 **15** 13) under the heading Haemangiectatic Hypertrophy of Limbs – Congenital Phlebarteriectasis and So-called Congenital Varicose Veins –

There is a kind of congenital or developmental hypertrophy and dilatation of arterial and venous trunks especially those of one of the upper limbs – a tumour like haemangiomatous overgrowth in the vascular system which may be I think roughly compared to conditions of plexiform (also called vermicular or cylindrical) neuroma (German Rankenneurom) – one kind of elephantiasis nervorum – in the nervous system Both the arteries and the veins of an extremity may be involved and sometimes the communication between the arterial channels and the venous channels may be so free that a definite kind of thrill or pulsation rhythmical with the heart s contractions is transmitted to the veins as in cases of arterio venous anastomosis of traumatic origin The condition is

tasis) of the whole left upper extremity The course of the arteries was normal and there was no abnormal communication to be discovered between arteries and veins Examination of the arteries showed only slight sclerotic changes The presence of an ascending pulse in the veins was explained as due to extreme dilatation of the capillaries connecting the arteries with the veins The humerus of the affected (left) side was longer by one centimetre than that of the normal (right) side and Bockenheimer compared this increased bony growth to the thickening of bones sometimes met with in cases of chronic valvular diseases of the heart

Ebstein [12] has met with three cases of phlebarteriectasis The first involved diffusely the whole left upper limb of a man aged 24 years and that extremity was 5½ cm longer than its fellow of the right side The second case was that of a girl aged 14 years whose right forearm was 3 cm longer than her left forearm The third case was that of a man aged 49 years His left upper extremity well shown in the photograph figured in Ebstein s account felt decidedly warmer than the right upper extremity and was an excellent example of phlebarteriectasis The left forearm was 2 cm longer than the right forearm There was no evidence of any cardiac disease or abnormality Ebstein speaks of these three cases as being the ninth tenth and eleventh described in the literature of the subject He regards the condition as mostly congenital and thinks that (as K O Weber pointed out) one of the upper extremities is more often affected than one of the lower extremities

A special kind of *congenital varicose veins in extremities* may possibly be due to congenital obstruction in the main venous trunks of the affected limbs Pierre Lereboullet [13] and Louis Petit at the Societe Medicale des Hopitaux de Paris (February 7 1914) demonstrated a case of the kind namely that of a man aged 52 years with congenital varicose veins of the left upper extremity The consequent progressive swelling and deformity was associated with a fragility of the bone evidenced by an ununited fracture of the forearm L H Petit [14] who is referred to by the above mentioned writers collected together in 1880 various examples of congenital *varicose veins of the arms possibly due to congenital obstruction in* the subclavian vein J Brau Tapie [15] in 1914 collected about a dozen cases of congenital varicose veins of the lower extremities in some of which capillary angiomata were likewise present An example of congenital varicose veins of the right lower extremity in a man aged 38 years was figured in 1914 by H Simon [16] The case

From what is known as congenital (or early developmental) trophoedema or trophic oedema of extremities (H Meige etc) which sometimes runs in families haemangiectatic hypertrophy of limbs may be distinguished by the absence in the former of the vascular abnormalities associated with the latter condition and likewise by the absence in the former of actual increase in the length of the bones of the affected limbs [1]

Amongst examples of congenital or developmental phlebarteriectasis with haemangiectatic hypertrophy of limbs I shall first allude to Sir Thomas Smith s case which he described in 1882 as one of Angiectasis of the Hands and Fingers [2] The patient was a female aged 25 years The affected hand was much larger than its fellow and its temperature higher *The subcutaneous tissue was occupied* by dilated and tortuous veins The arteries of the fingers hand and forearm were greatly enlarged and somewhat tortuous When the hand was lightly grasped a purring thrill could be felt According to *the mother the hand seemed normal till the patient was one and a* half years old

H Braun [3] and his pupil Lawen [4] have contributed valuable papers (1902 and 1903) on the subject The latter explains the con *dition of general diffuse phlebarteriectasis as a spontaneous or* idiopathic progressive dilatation of the blood vessels of the affected portion of the body the dilatation involving the arteries capillaries and veins of the part he thinks however that the process is *not associated with any actual new formation of blood vessels Lawen gives* a very detailed account of the case demonstrated by H Braun in November 1901 before the Medical Society of Leipzig The patient was a man aged 43 years whose right upper extremity had been *more or less affected by the phlebarteriectasis from childhood and* the case was a typical one Lawen has carefully reviewed and classified earlier cases described by Letenneur (1859) [5] Krause *(1862)* [6] Nicoladoni (two cases *1875 and 1877)* [7] A Obalinsky and *T Browicz (1875) [8] and Fischer (1880) [9] It was* Karl Otto Weber [10] who first separated off the group of cases which he called Genuine Diffuse Phlebarteriectasis and in which there is not necessarily any abnormal arteriovenous anastomosis present from the well *known traumatic cases of varicose aneurysm* connected with abnormal arteriovenous anastomosis In phlebarteriectasis he said the affected extremity was generally an upper not a lower one

Philipp Bockenheimer [11] in 1907 carefully described an example of genuine diffuse *phlebectasis* (as opposed *to phlebarteriec*

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I now feel certain that some cases of congenital or developmental hemihypertrophy are of the same nature as what I call haemangi ectatic hypertrophy of limbs A possible example of the type of case to which I refer was shown by M W Arthurton (for David Levi) at the Paediatric Section of the Royal Society of Medicine on January 28 1949 The patient is a boy aged 4 years with enlarge ment of face ear nose palate cornea and pupil on left side The left eye is prominent but the fundi are both normal There are

of congenital elephantiasis of the right arm in a child [17] described and figured by C T Dent in 1910 might have been due to congenital obstruction in the main venous channel of the affected limb or possibly it was a genuine example of congenital phlebarteriectasis but the condition seems to have been associated with extensive lymph angiectasis and with cavernous angioma

The following cases may represent *lesser forms of true phleb arteriectasis* At the Society for the Study of Diseases in Children C O Hawthorne [18] in 1902 showed a boy aged 10 years with hypertrophy of the right lower limb which was 3 cm longer than its fellow The skin of the right foot and of the right leg was unduly warm the veins were prominent and the arteries both in front of and behind the ankle joint were apparently dilated On the dorsum of the foot were certain patches which gave rise to some discussion but which in my opinion were haemangiomatous or partly lymph angiomatous At the same Society in the same year A B Roxburgh [19] showed a female child aged 5 years with varicose veins of the left lower extremity and a large cavernous angioma on the outer side of the left knee There was slight alteration in the length and shape of the tibia on the affected side At the Clinical Society of London in February 1903 T H Kellock [20] showed a female child aged 8 years with a varicose condition of the right internal saphenous vein the right leg was rather more than 1 cm longer than the left

About 1907 I saw a case of a somewhat different class The patient was a child aged 12 weeks with a condition of diffuse superficial cutaneous angioma involving nearly all the left side of the body and the left limbs and most of the head The left upper and lower limbs were decidedly larger in circumference than the right ones but (as yet) there was no obvious difference in length between the corres ponding long bones of the two sides [21] With this case may be compared one described by J Fletcher Little (in 1893) of a girl aged 15 years who had been born with a condition of diffuse superficial cutaneous angioma involving nearly the whole of the right half of the body The bones of the right extremities were longer than those of the left the right leg measuring about 5 cm in length more than its fellow [22] The increased size of limbs associated with the angiomatous conditions in these last two cases doubtless borders on the class of angio elephantiasis as described long ago by Virchow and Hebra

XXXIX

A NOTE ON SO CALLED CONGENITAL VARICOSE VEINS[1]

F PARKES WEBER

In the *British Journal of Children s Diseases* 1918 **15**, 13–17 I wrote a short paper entitled Haemangiectatic Hypertrophy of Limbs—Congenital Phlebarteriectasis and so-called Congenital Varicose Veins The cases which I collected in that paper were not all strictly of the same nature I showed however that apart from true local gigantism in which the excess of growth is altogether monstrous (e g giant fingers or giant toes giant feet or giant hands) there exists a somewhat mixed group of cases in which one or more limbs are abnormally large and are associated with the presence of vascular (haemangiectatic often telangiectatic) naevi either in the hyper trophic limbs or in other parts of the body In all the typical cases of this group which I collected the hypertrophic limbs and the bones of the segment or segments involved were not merely larger but also longer than their fellows I suggested that the haemangiectatic con dition in all such cases was in some way aetiologically connected with the increase of growth and one must remember that increase in length of bones not rarely results from the increase of blood supply due to chronic local inflammatory conditions in growing children such as the now relatively rare deforming chronic osteitis of inherited syphilis (cf F Parkes Weber *British Journal of Children s Diseases* 1908 **5**, 83) Large limbs of the Nonne Milroy Meige class were I thought to be excluded from this group for they never showed increase in length of bones

In some such cases congenital varicose veins were connected with and constituted a part of this developmental disturbance of growth, and were associated with a telangiectatic or other haemangiectatic naevus formation It is only with such so-called congenital varicose veins that I am concerned in the present account

Such congenital varicose veins are really only large or giant veins of developmental origin but are not strictly speaking true varicose veins i e veins with the special alteration in the vessel walls found in true varices and which are due to insufficiency of vein valves and chronic distension of postural origin (acting on a predisposed basis) The large size of these giant veins is due I believe to a develop mental enlargement strictly analogous to the developmental enlarge ment of the capillaries which is the cause of a cutaneous port wine naevus (naevus flammeus) or any variety of telangiectatic naevus

[1]From the *British Journal of Children s Diseases* (1936) 33 10?

several port wine stains on the trunk and a nodule of uncertain nature above the left eye The left arm and leg are longer than the right and there is valgus deformity of the right ankle However subsequent biopsy of left cheek showed plexiform neurofibroma (*Proc* 1949 **42,** 562)

Since my original paper (1918) on haemangiectatic hypertrophy many reports on the same subject have been published in some of which my name has been used in the title I will merely mention the following Sir Archibald Gray *Proc Roy Soc Med* 1928 **21,** 65 Pautrier and Ullmo *Annales de Dermat* 1929 **9,** 1195 E Susman *Med Journ Australia,* 1927 2 581 H L Blumgart and A C Ernstene *Arch Int Med* 1932 **49,** 599 E Bizzozero *Giorn Ital di Derm e Sifilo* 1935 **76,** 969 V Pardo-Castello *Urol and Cutan Journ* 1937 **41,** 446 De Witt Lewis *Lancet* 1930 **2,** 621 B T Horton *Journ Amer Med Assoc* 1932 **98,** 373 Harris and Wright *Heart* 1930 **15,** 141 Paterson and Wylie *Brit Journ Child Dis* 1925 **22,** 36 B S Simpson *Edinb Med Journ* 1926 New series **33** 623 P P Reickenheim *St Barth Hosp Journ* London War series 1943 **4,** 53 (with many references) Caletti and Resta *Arch Ital Derm* 1948 **20,** 262 Poinso Marcorelles and Charpin *Presse Med* 1946 577 P Ghiso and others *Revista Argentina de Dermatosif* 1938 **22,** 203

Besides this the boy shows a condition of what may popularly be termed congenital varicose veins the position of which in the right inguinal region is well shown by fig 4 from a drawing by Mr W Thornton Shiells

In conclusion I would repeat that *such so called congenital varicose veins' are not strictly speaking true varicose veins but are examples of a developmental enlargement of veins analogous to the developmental enlargement of cutaneous capillaries in any superficial telangiectatic naevus*

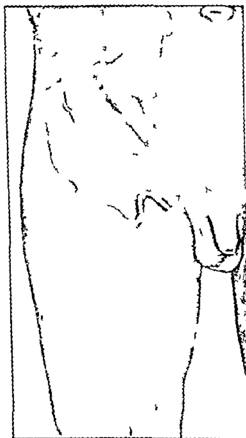


FIG 4

ADDENDUM—For recent papers on congenital varicose veins *see* G W Bamber (1937) *Proc Roy Soc Med* 30 521 and R Klaber (1940) *ibid* 33 581

To further explain what I mean by the term *congenital varicose veins* I will cite the case of a boy (S A) aged 7 years whom I have lately observed Except for his haemangiectatic abnormalities which are of congenital origin he seems normally developed in body and mind The mother as usual gives a history of maternal impression At about the sixth week of pregnancy she was frightened by a rat which made her go all of a shake There is no history of haemangiectatic or any congenital abnormality of development in any other member of the family and there is no consanguinity between the parents

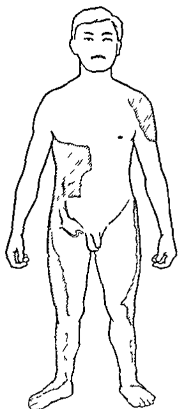


Fig 1

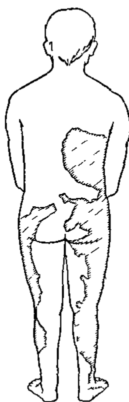


Fig 2

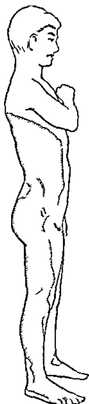


Fig 3

The most striking feature in the boy s appearance is the widely spread superficial telangiectatic naevus of the trunk and lower limbs the distribution of which is well illustrated by the accompanying semi diagrammatic figures (figs 1 to 3) This extensive naevus is not quite symmetrically situated on the two sides of the body but may perhaps be termed a systematized *bilateral* naevus unius lateris

118 197 and ibid 1945 suppl 158) or restless legs I believe myself that the irregular motor discharges causing the myoclonic movements are often connected with some temporary irritative disturbance in the gastro-intestinal system

Another paroxysmal painful condition the cause of which remains disputed in spite of much discussion is proctalgia fugax Little had been written about this before the article on the subject (*Lancet* 1935 2, 243) by T E H Thaysen of Copenhagen This was followed by much correspondence and it seemed that many doctors had themselves suffered from at least one attack According to Sir Arthur Hurst (*Proc Roy Soc Med* 1943 36 639) the seat of the pain is in the rectum and neither in the pelvic colon nor in the anal canal *Beginning as an ache the pain rapidly increases in severity and may* finally be agonizing and cause profuse sweating the patient becoming pale and cold and occasionally breathless He may even lose consciousness The pain has a peculiar gripping character which is always the same though it may vary in intensity in different attacks It is generally nocturnal waking the patient in the early morning without having given any warning the previous evening I think that the pain of paroxysmal proctalgia is only one variety of pain in the viscera due to spasmodic contraction of unstriped muscle There may possibly be various reflex exciting causes but in some cases the disturbance is possibly idiopathic Only a few individuals seem to be developmentally so constituted that in adult life they suffer from many kinds of severe abdominal pains – apparently all due to cramp-like contraction of unstriped muscle – induced by local exciting causes probably mostly on the basis of mental fatigue or emotional disturbance

XL

THE INTERPRETATION OF PHYSICAL HAPPENINGS IN THE BODY BY THE SUBCONSCIOUS AND BY THE FULLY CONSCIOUS BRAIN

F PARKES WEBER

It is fairly obvious that certain nightmare or other dream sensations are the result of misinterpretation of various physical happenings in the abdomen or other parts of the body by a brain that is sleeping or not fully conscious Such are the sensation of falling and many unpleasant dream experiences which wake the sleeper up On awakening sometimes there is a pain or disagreeable sensation in the abdomen or elsewhere in the body which usually quickly passes off but which whatever its cause may be supposed to have caused the dream sensation which immediately preceded awakening In other words the abdominal or other disturbance being wrongly interpreted by the subconscious or not fully conscious brain was the cause of the disturbing dream sensation in question I am one of those who believe that a process of this kind is the most plausible explanation of most ordinary nightmares

But do we know the exact cause of many painful or disagreeable sensations felt by us in our ordinary fully conscious state? Of some fairly ordinary ones we certainly do not know the exact cause We do indeed know something of the causation of the sensations of angina pectoris of cramp-like attacks of intermittent claudication of extremities of carotid sinus and vaso-vagal sensations of some head aches and of angor animi But of the exact causation of many other fairly ordinary pains and disagreeable sensations we know hardly anything Even the exact explanation of the ordinary stitch in the side felt by children and young persons on running after meals is still uncertain Then there is the sudden and transient stabbing (transfixing) pain through a lung—felt by young persons apparently in perfect health I will not enter into any discussion on so-called growing pains in bones

One of the most interesting questions is the nature of the paraesthesiae sometimes associated with the common myoclonic movements in the lower limbs from which some persons often suffer on becoming warm in bed especially when they have not been moving their legs much during the day This common complaint has lately been termed Ekbom s syndrome (K A Ekbom *Act Med Scand* 1944

118 197 and ibid 1945 suppl 158) or restless legs I believe myself that the irregular motor discharges causing the myoclonic movements are often connected with some temporary irritative disturbance in the gastro-intestinal system

Another paroxysmal painful condition the cause of which remains disputed in spite of much discussion is proctalgia fugax Little had been written about this before the article on the subject (*Lancet* 1935 2, 243) by T E H Thaysen of Copenhagen This was followed by much correspondence and it seemed that many doctors had them selves suffered from at least one attack According to Sir Arthur Hurst (*Proc Roy Soc Med* 1943 36 639) the seat of the pain is in the rectum and neither in the pelvic colon nor in the anal canal Beginning as an ache the pain rapidly increases in severity and may finally be agonizing and cause profuse sweating the patient becoming pale and cold and occasionally breathless He may even lose con sciousness The pain has a peculiar gripping character which is always the same though it may vary in intensity in different attacks It is generally nocturnal waking the patient in the early morning without having given any warning the previous evening I think that the pain of paroxysmal proctalgia is only one variety of pain in the viscera due to spasmodic contraction of unstriped muscle There may possibly be various reflex exciting causes but in some cases the disturbance is possibly idiopathic Only a few individuals seem to be developmentally so constituted that in adult life they suffer from many kinds of severe abdominal pains—apparently all due to cramp-like contraction of unstriped muscle—induced by local exciting causes probably mostly on the basis of mental fatigue or emotional disturbance

XLI

ZEST IN OLD AGE

REVIEW BY F PARKES WEBER[1]

In the ages of mediaeval Christian faith a good death was regarded as the crown of life (not necessarily always of a good life) Nowadays surely a healthy old age with true ripeness and preservation of the intellect has a just claim to be called the crown of an active and well spent life Among the many (including some brilliant) medical and philosophical books and essays on old age there is not one, so far as I know really similar to Dr Vischer s Dr Vischer who has had exceptional opportunity at Basle for a long and obviously sympathetic study of old persons gives us the result of his experience and study regarding their physical and psychical peculiarities and infirmities their mental life and how best to make them comfortable and happy in the feeling that they are still really playing a useful part in life

Paediatrics in spite of considerable opposition gained recognition as a medical specialty and now with the greatly increased proportion of *old* persons among the public geriatrics can no longer be denied a place

When about 20 years of age I once had the privilege of sitting at dinner next to the warm hearted Sir James Paget He questioned me on how I spent my holidays and then he gave me to understand that I was one of those who preferred change of work to mere rest or amusing games—I suppose he included the strenuous pursuit of hobbies under change of work Change of work doubtless gives a temporary holiday to groups of brain cells—according to the ideas admirably put forward by the late Sir Farquhar Buzzard (1928) quoted with approval by Dr Vischer (p 192) and these ideas should be remembered in the management of some of the troubles of late middle age and commencing senescence Old persons should not be discouraged from making harmless experiments in regard to way of life (including diet) if they find that for a time their vigour and zest in life are *thereby increased*

One need scarcely mention that when long periods of continuous physical and mental work become impossible the experience of old persons is often still so useful that they should be recognized as

[1]From *British Medical Journal* 1948 1 501 Review of Dr A L Vischer s book Old Age Its Compensations and Rewards G Allen and Unwin 1947

advising or consulting authorities (not sleeping partners) For instance in our medical profession they might often be made active consultant diagnosticians to hospitals and institutions where they were formerly on the regular visiting staff

The clear wording and admirable translation of Dr Vischer s book should be specially noted but not the least feature is its wealth of references to sparkling and appropriate epigrammatic sayings and discussions by previous writers of all kinds bearing on a subject which perhaps next to love and death offers itself most readily to literary artists One piece of advice from early mediaeval Christianity (not included in the book) I once stumbled on—namely the last two lines of a letter by Paulinus Bishop of Nola early in the fifth century (eleventh volume of Migne s *Patrologia series latina* column 184) Vive precor [another version gives Vive diu] sed vive Deo nam vivere mundo Mortis opus vera est vivere vita Deo In the widest possible humanistic spirit I think one should interpret these lines Live long the fullest life you can but live as rightly as you are able to for to do wrong is death s work to act rightly is the true life to God

SUBJECT INDEX